S. Hrg. 100-567

"NUTRASWEET"—HEALTH AND SAFETY CONCERNS

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

ONE HUNDREDTH CONGRESS

FIRST SESSION

ON

EXAMINING THE HEALTH AND SAFETY CONCERNS OF NUTRASWEET (ASPARTAME)

NOVEMBER 3, 1987

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"NUTRASWEET"—HEALTH AND SAFETY CONCERNS

TUESDAY, NOVEMBER 3, 1987

U.S. Senate,
Committee on Labor and Human Resources,
Washington, DC.

The committee convened, pursuant to notice, at 9:40 a.m., in room SD–430, Dirksen Senate Office Building, Senator Howard M. Metzenbaum, presiding.

Present: Senators Metzenbaum and Hatch.

OPENING STATEMENT OF SENATOR METZENBAUM

Senator Metzenbaum. Sorry we are a little late.

It has been hailed as the most successful food additive in history. One hundred million Americans use it. It commands over $700 million in sales. Over 20 billion cans of diet soft drinks containing it are sold each year. And it seems to be in everything—cereal, kids' vitamins, cocoa, puddings, even over-the-counter drugs.

There is no doubt about it. NutraSweet has captured the hearts and the tastebuds of the American consumer.

And why not? It tastes great, contains few calories, and does not cause tooth decay in children. NutraSweet is the dream product. But for some consumers and scientists, the dream may be too good to be true.

The FDA has received close to 4,000 consumer complaints, ranging from seizures to headaches to mood alterations. Studies and letters in the medical journals have warned of possible neurological and behavioral effects in humans, particularly in children and susceptible individuals.

Dr. Richard Wurtman, of MIT, has warned of a potential link to seizures.

Dr. William Pardridge, of UCLA, has raised concerns about excessive consumption by children.

Dr. Louis Elsas of Emory University is worried about possible risks to pregnant women.

Dr. Michael Mahalik at the Philadelphia College of Osteopathic Medicine warns of the possibility of brain dysfunction.

Dr. Reuben Matalon, at the University of Illinois, has warned about potentially dangerous long-term effects on learning ability.

Dr. Jeffery Bada, a professor of chemistry at the University of California, states that NutraSweet's decomposition products have not been adequately studied.

Dr. Roger Coulombe, of Utah State, has cited NutraSweet's possible behavioral and neurological effects and called for new research.

In response to these concerns raised in the scientific community, we hear that NutraSweet is the most tested food additive in history, proven safe in over 100 studies that were used for FDA approval.

What we do not hear too much about is the controversial history of a number of those much-vaunted studies, studies which an FDA investigative team once described as "seriously deficient, scientifically compromised, and irresponsible"; studies which the FDA's chief legal officer once wanted investigated by a grand jury, the first such request in the agency's history; studies which a public board of inquiry found to be inadequate on the issue of brain tumors; studies which three FDA scientists called into question just weeks before a new FDA Commissioner approved NutraSweet in 1981.

Any FDA approval is a scientific judgment call. We all know that. Frankly, I think there is doubt about whether they made the right call. At my request, the GAO investigated and said the FDA followed its approval process. But they did not evaluate the scientific controversy surrounding the tests.

Today we will hear from a former FDA toxicologist who examined some of those key tests and believes there is still reason to be concerned about their credibility.

But the question before this Committee is where do we go from here. I am hopeful that this hearing will produce results. We need new, independent tests of safety. We don't need the company or nonprofit institutes fronting for the company, telling us that this product is safe. I hope that message comes across loud and clear here today. We should have clear, understandable labelling that tells people how much NutraSweet is in their diet soft drink, or pudding, or cereal. We should be informed about the limits recommended for consumption.

There should be an FDA hotline for consumer complaints and mandatory reporting of such complaints by the manufacturer to the FDA.

Finally, we should learn a lesson from the NutraSweet experience. If a food additive has potential neurological or behavioral effects, it should undergo human clinical testing, similar to the process a drug must undergo before it is put on the market. Only animal tests were required of NutraSweet, though at one point in the approval process, FDA scientists had recommended that NutraSweet be tested like a drug. They were overruled. I wish they had not been. Maybe a number of questions before the Committee today would have already been answered.

These are among the issues I hope to examine at this hearing. Today we will hear from consumers who believe they have experienced severe reactions to NutraSweet, and a physician who has observed such reactions in his practice. We will hear from scientists on both sides of the controversy and from the Commissioner of the Food and Drug Administration.

We will hear from a consumer attorney who is not only concerned about NutraSweet, but also about the way basic research on the safety of foods is conducted in this country.

Finally, we will hear from the President of NutraSweet, Mr. Robert Shapiro. I have met Mr. Shapiro previously. In fact, we have engaged in lengthy negotiations earlier this year on getting new, independent tests of safety. We haven't gotten there yet. I believe that the company was above-board and negotiated in good faith. However, we reached an impasse when it came to who would do the research.

I am frank to say that the NutraSweet Company, the food and beverage industry, and their various institutes, exert tremendous influence over scientific research and investigation. I want to make sure such work is genuinely independent.

I do not believe that scientists who have raised concerns about safety should be excluded from the process, and I am hopeful that the company will see fit to reopen these negotiations following this hearing.

In conclusion let me say this. I know that diabetics and others in this country need artificial sweeteners. I want them to have them. I just want to be sure that an artificial sweetener like NutraSweet that is being consumed by so many people in such vast amounts is safe beyond doubt. I do not have that confidence sitting here today.

At this point I will insert in the record the prepared statement of Senator Thurmond.

[The prepared statement of Senator Thurmond follows:]

STATEMENT BY SENATOR STROM THURMOND (R.-S.C.) REFERENCE FULL SENATE LABOR COMMITTEE HEARING ON NUTRASWEET, TUESDAY, NOVEMBER 3, 1987, 9:30, SD-430.

MR. CHAIRMAN:

I am pleased to attend this hearing on Nutrasweet. Certainly, protection of the public health is a paramount concern to us all.

It is my understanding that the Food and Drug Administration has received over 3,600 consumer complaints since this product was introduced in the market. Moreover, I have seen figures stating that over 5 million pounds of this sweetner enter the food supply every year.

Mr. Chairman, the Nutrasweet Company stands by its product. It asserts that this product is safe.

Accordingly, I am pleased we are having a hearing on this issue and I intend to listen carefully to all sides.

Mr. Chairman, I have recently received correspondence from one of my constituents, Ms. Doris Bookhart, about her medical problems which she believes are associated with Nutrasweet. I ask that her letter and accompanying documents be included in the record.

Mr. Chairman, while my schedule may not permit me to stay for the entire hearing, I look forward to following this matter closely.

Senator METZENBAUM. Our first panel consists of Commissioner Frank Young. Commissioner, are these gentlemen all with you?

Commissioner YOUNG. Yes.

Senator METZENBAUM. Fine. You may introduce them if you like. And, as I indicated to you, Commissioner, I want to be sure I get to all the witnesses today, and Mr. Shapiro is the last witness on the list and I do not want to foreclose him, so I would ask you to hold your remarks to 10 minutes, no longer than 15 at the most.

STATEMENT OF HON. FRANK YOUNG, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY JOSEPH A. LEVITT, EXECUTIVE ASSISTANT; RICHARD J. RONK, ACTING DIRECTOR, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION; DR. ALLAN L. FORBES, DIRECTOR, OFFICE OF NUTRITION AND FOOD SCIENCES, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION; DR. DAVID G. HATTAN, CHIEF, REGULATORY AFFAIRS STAFF, OFFICE OF NUTRITION AND FOOD SCIENCES, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, AND THOMAS SCARLETT, CHIEF COUNSEL, FOOD AND DRUG DIVISION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Commissioner YOUNG. Thank you very much, Mr. Chairman.

I would like to introduce the panel I have brought with me so you will have ample individuals from the Food and Drug Administration to be able to answer some of the questions you have posed and some of the interests that the American people have had in this important issue.

On my far right is Dr. Allan Forbes, who is Director of the Office of Nutrition and Food Sciences. Next to him is Mr. Richard Ronk, who is the Acting Director of the Center for Food Safety and Applied Nutrition. On my immediate right is Tom Scarlett, our General Counsel. On my immediate left is Dr. Dave Hattan, who is the Chief of Regulatory Affairs Staff of the Center for Food Safety and Applied Nutrition. And on his immediate left is Mr. Joseph Levitt, who is Executive Assistant to the Commissioner.

I genuinely appreciate this opportunity to be present at this Congressional hearing. As you know, NutraSweet has been subjected to intense investigations, and I would like, Senator, to provide some background to try to walk through and set some of the framework for the discussion today. I shall therefore focus on the displays that I have brought with me.

[Information supplied for the record follows:]

Submission for the Record

ASPARTAME

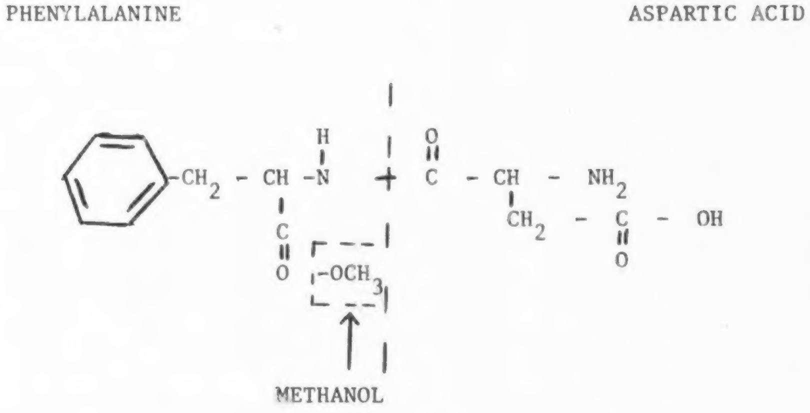
Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: Display Charts:

A. Molecular structure of aspartame.
B. Aspartame adverse reactions (1986-87).
C. Intakes of aspartame in perspective.

FOR ASPARTAME
AND ITS DIKETOPIPERAZINE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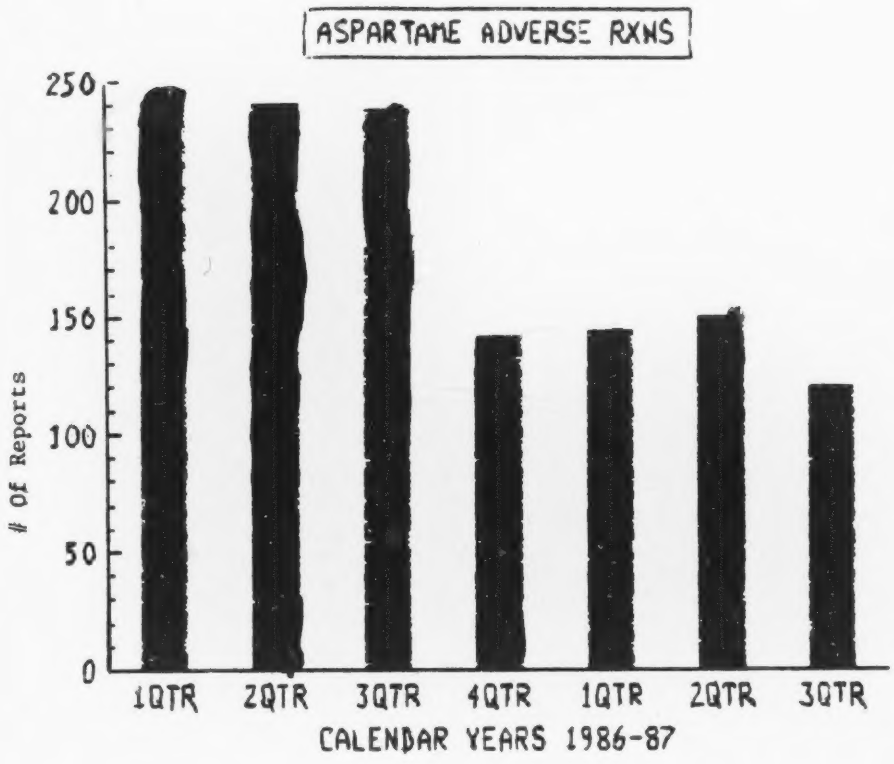
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# Of Reports
1QTR
2QTR
3QTR
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3QTR
CALENDAR YEARS 1986-87

Intakes of Aspartame in Perspective

No Effect Level (from life-time animal studies)	2,000 - 4,000 mg/kg (USA) (JECFA/WHO-FAO)		
	↓		
Acceptable Daily Intakes (safety factors applied to animal and/or clinical studies)	20 - (early USA)	40 - (Canada)	50 mg/kg (current USA)
	↓		
Actual Intakes (MRCA data) (90th percentile)	2 - 4 mg/kg		

Commissioner YOUNG. The molecule that we are focusing on, aspartame, is composed of the amino acids phenylalanine and aspartic acid, and it has a methanol group which is shown here. This has a substantial advantage in sweetness, on a per-weight basis, to carbohydrate sweeteners.

During this period of time, we have focused on a number of issues to try to look at the safety of this. And you have displayed here the data that we have provided for you in our interactions, that show the relative consumer complaints that we have received.

This is a passive system in which we ask for consumers, physicians and others to send in complaints to us. As a matter of fact, as an additional layer of safety, I had published in the Drug Bulletin in 1985 a call to individuals who are physicians to send in complaints, and I would like to submit that for the record.

[Information supplied for the record follows:]

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HEALTH & HUMAN SERVICES

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Food and Drug Administration (HFI 42)
Rockville MD 20857

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Food and Drug Administration
200 C Street, S.W. (Rm. 3321)
Washington, D.C. 20204

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28 JAN 1986

FDA Drug Bulletin

December 1985 Volume 15 Number 4

Request For Reports Of Food Adverse Reactions

Aspirin For Heart Patients

Emergency Use Of Unapproved Medical Devices

Problems With Large Size 60° Convexo-Concave Heart Valves

Unapproved Use Of Minoxidil

Genetically Engineered Human Growth Hormone Approved

Approval Of Implantable Defibrillator

Inactive Ingredients Listed In Labeling

Reye Syndrome Update

Recommendations Of DES Task Force

Class I Recall

Correction

FDA Drug Bulletin

Information of Importance
To Physicians and
Other Health Professionals

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Editor: Judith Willis

Request For Reports Of Food Adverse Reactions

Physicians and other health professionals are asked to inform FDA of any severe and well-documented non-microbiologic reactions associated with food.

FDA's Center for Food Safety and Applied Nutrition (CFSAN) is currently monitoring adverse reactions due allegedly to sulfiting agents and aspartame and wishes to receive reliable information on serious reactions that appear to be strongly associated with these or similar food additives, foods, and dietary practices or products.

CFSAN has recently redesigned and expanded its post-marketing surveillance system for identifying adverse reactions to food products and additives. The new components were devised to more adequately identify and evaluate complex adverse reaction complaints received by FDA district offices on aspartame-containing products and on sulfiting agents in foods.

This new post-marketing surveillance component will function as an adjunct to CFSAN's routine monitoring of injury/illness reports due to microbial contamination and adulterated food products. It is not designed to duplicate efforts of state reporting systems and the reporting system of the Centers for Disease Control (CDC), all of which primarily monitor microbial food reactions.

In addition, FDA has formed a Committee on Hypersensitivity to Food Constituents that is currently reviewing the classification of adverse reactions to foods and is formulating criteria for these reactions.

Health professionals who become aware of non-microbial reactions to foods are asked to complete and return the Drug Experience Report on the back of this *Drug Bulletin*.

Commissioner YOUNG. As you can see, the vast majority of these are in the form of soft drinks, and then you see the variety of usage here.

We follow this on a quarterly basis. We have analyzed in excess of 3,500 of these complaints, and you can see the per quarter, first quarter of 1986-87, second quarter, third quarter, fourth quarter, and then the quarters to date at this time.

With the amount of usage that we have, it is important to emphasize that this is, though passive, a relatively low incidence of adverse reactions for a compound that has been in such extensive usage, as we point out, by millions and millions of people.

As we analyze these, the vast majority of complaints that we have found were complaints that focused on the very mild and nondescript syndromes—headaches, dizziness at times, upset stomach. None of these were a sentinel focus that would say "yes," this is a particular symptom and sign associated with disease.

When I was in the great State that you represent, Ohio, I functioned as a pathologist; I was involved in occasional coroner cases. And when we looked at cases from a standpoint of adverse reactions, we had to be very careful to go to the medical records and to examine these and try to look at signs and symptoms.

As we view these number of cases, as they come in as a function of time, when we have gotten the medical records, we have not been able to make a link between any particular cause and effect with these symptoms. But nevertheless, not wanting to leave any stone unturned, in Action Plan Phase II, which I shall submit for the record, we are strengthening our adverse reaction reporting not only in drugs, biologics, but also in food.

[Information supplied for the record follows:]

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: Food and Drug Administration, A plan for Action Phase II

FOOD AND DRUG ADMINISTRATION

A PLAN FOR ACTION

PHASE II

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

This announcement of Phase II of FDA's Action Plan marks a milestone in FDA's history: The first time the Agency has implemented back-to-back agency-wide action plans. Coming, as it does, on the heels of FDA's most productive year ever, we think this announcement bodes very well for the future. Such careful planning and husbanding of resources are essential to the Agency's future in view of the challenges facing us, particularly the AIDS crisis and the need to enhance the approval of new drugs for life threatening and serious illnesses. This document represents the best professional judgement of FDA and articulates a commitment to maximize FDA's effectiveness. FDA's efforts may need to deviate from this plan, however, because of competing priorities and the availability of resources.

In implementing Phase I and in crafting Phase II, we are thankful for the dedicated commitment and accomplishments we have received from FDA's Centers for Drugs and Biologics, Devices and Radiological Health, Food Safety and Applied Nutrition, and Veterinary Medicine, FDA's National Center for Toxicological Research, the FDA Office of Regulatory Affairs, the FDA Associate Commissioners and our staffs, especially FDA's Office of Planning and Evaluation.

We are also especially thankful for the strong support we have received from HHS Secretary Otis R. Bowen, M.D., Undersecretary Don M. Newman, J.D., Chief of Staff Thomas R. Burke, Assistant Secretary for Health Robert E. Windom, M.D., Surgeon General C. Everett Koop, M.D., and Deputy Assistant Secretary for Health Lowell T. Harmison, Ph.D.

Frank E. Young
Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

John A. Norris
John A. Norris, J.D., M.B.A.
Deputy Commissioner of
Food and Drugs

May 1987

A PLAN FOR ACTION
PHASE II

MAY 1987

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, Maryland 20857

FOREWORD

This document records a second major undertaking by FDA to significantly enhance its support of important public health initiatives. I am pleased to commend, on behalf of the Public Health Service, this commitment to action by FDA under the outstanding leadership of Commissioner Frank E. Young, M.D., Ph.D. and Deputy Commissioner John A. Norris, J.D., M.B.A.

July 1985 marked the announcement and initiation of implementation of FDA's Action Plan Phase I. The overwhelming success of the Action Plan is well documented and action planning has now become an established management and motivational process in FDA. But the success of the Action Plan goes even beyond the fact that the Agency has been faithful to its commitments and has to date successfully completed more than 85% of the 258 individual milestones (contracts) that were part of the plan. (The remaining 15% are longer term commitments, not yet due for completion.) Broader substantive accomplishments have occurred in every area of FDA's activities as a result of implementing the Action Plan. Specific examples of both are abundant.

FDA has succeeded in improving the timeliness, effectiveness, and efficiency of the new drug review process including: progress in reviewing new therapies for AIDS and other major new therapies on a 1-AA fast track; expediting completion of action on new drug application (NDA) efficacy supplements (including cutting the backlog by more than 30%); making major strides on product reviews of new drugs, biologicals, and generic drugs; and approving a record number of major biotechnology medical advances.

The medical device program achieved successes in the development of exemption criteria for devices categorized as Class I 510(k)s, in the improvement of the premarketing approval process for post-amendment Class III devices, in the reduction in the backlog of applications, and in the improvement of both headquarters and field capabilities to review devices combining microelectronics and microprocessors.

Postmarketing surveillance processes in drugs and devices were improved by increasing the quality and quantity of drug reporting from health professionals; by broadening the adverse drug reaction (ADR) reporting requirements to cover all prescription drugs; by incorporating new information technologies into the ADR system to facilitate efficient processing, retrieval, and analysis of ADR data; and by monitoring and evaluating the implementation of the Medical Device Reporting (MDR) regulations.

A new technique was developed for risk analysis by using intergovernmental panels to focus on risk assessments in colors and publishing each assessment prior to finalizing the risk management decision.

FDA improved risk management processes by: completing a thorough assessment of current risk management procedures; by developing guidelines for the preparation of effective enforcement strategy statements for new regulations; by implementing a more efficient regulation development process; and by completing several reviews of field resources to more efficiently and effectively deploy them.

In the food safety area, FDA was able to move strongly forward with appropriate application of *de minimis* (a principle of law stipulating that the law does not concern itself with trifles). A food chemistry program was established to increase the Agency's knowledge of the composition, interactions, and transformations in the food matrices of dietary components.

FDA successfully accomplished significant activities in helping the consumer to cope with products with fraudulent health claims. These involved significant numbers of national speeches and press interviews on how to recognize and to avoid health fraud involving economic fraud or direct or indirect health hazards. These also involved efforts to expand national awareness on health fraud through education including: holding three regional health fraud conferences in Orlando, Detroit, and Los Angeles; sponsoring a widely attended National Health Fraud Conference in Washington, D.C.; expanding local coalition efforts by holding health fraud conferences in each of FDA's 21 districts; issuing jointly with the Better Business Bureau an alert on weight reduction to provide the media with information to detect misleading advertising; developing a public awareness campaign with the Pharmaceutical Advertising Council; and conducting special health fraud education programs for selected target populations (e.g., a Hispanic Health Fraud Conference). Intergovernmental cooperation was enhanced by planning and conducting district/regional training seminars for state and local officials, the Federal Trade Commission and the U.S. Postal Service.

Finally the Agency accomplished a number of internal management improvements including: implementation of the Commissioner's Advancement Program (a program to advance the careers of employees and the goals of the Agency simultaneously), development of a more coordinated information management system for the Agency including a state-of-the-art application tracking system, completion of several administrative practices reviews, establishment of a comprehensive facilities plan, and increased Agency communications with women (including the sponsorship of a widely attended national women's health conference), the elderly, minorities, and handicapped.

The 11-point plan of action described in this document as Action Plan Phase II (APPII) represents a well conceived set of public health initiatives which will contribute significantly to identifying, preventing, and resolving important public health problems. The Secretary of Health and Human Services Otis R. Bowen, M.D., has emphasized the importance of these initiatives and has provided FDA valuable support toward their accomplishment. The Public Health Service is pleased to add its support and encouragement to this important undertaking, and I personally wish FDA, Commissioner Frank Young, and Deputy Commissioner John Norris every success in its implementation.

Robert E. Windom, M.D.
Assistant Secretary for Health

EXECUTIVE SUMMARY

Action Plan Phase II (APPII) supports, by action, the important public health problem identification, public health problem prevention, and public health problem resolution initiatives of the Public Health Service (PHS) and the Department of Health and Human Services (HHS). APPII builds on the successes of Action Plan Phase I and charts a broad program of concerted action to fulfill FDA's important public health mission. The plan was developed through an intensive and participative process involving Commissioner Frank E. Young, M.D., Ph.D., Deputy Commissioner John A. Norris, J.D., M.B.A., FDA's Policy Board, many subordinate levels of FDA employees, experts from FDA's Office of Planning and Evaluation, and experts from outside the Agency. Initiatives developed by HHS Secretary Otis R. Bowen, M.D. and Assistant Secretary for Health Robert E. Windom, M.D. have brought a department-wide scope to the actions being undertaken by FDA. APPII involves an 11-point program of action, summarized as follows:

1. **Acquired Immunodeficiency Syndrome (AIDS).** The AIDS epidemic has been identified as the President's number one public health priority. FDA will place special emphasis on producing the most timely, effective, and efficient research and premarketing review possible of products that offer promise for treating, curing, or preventing AIDS or AIDS-related diseases. Particular emphasis will be given to advising sponsors on the regulatory process, to upgrading productivity by focusing on rate-limiting steps in the review process, and to conducting research that will contribute to enhancing the product review processes both for drugs and for vaccines.
2. **Premarketing Product Evaluation.** FDA will increase its efforts in improving the premarketing evaluation processes for drugs and devices, begun during Action Plan Phase I. Particular emphasis will be given to the recruitment and training of personnel for the reviewing divisions and on methods to enhance retention of existing review personnel. Recognizing the importance of scientific research in the reviewing divisions, FDA will enhance its scientific expertise in biologics, devices, and drugs. Additional improvements are expected to be achieved through clarification and modification of review procedures and through implementation of the investigational new drug application/new drug application (IND/NDA) rewrite. Of particular note is the proposal to enhance the use of treatment INDs for desperately ill patients with immediately life threatening diseases and for those with serious diseases. To accomplish this, FDA is reproposing procedures to make investigational new drugs available to patients as early in the drug development process as possible. These procedures will apply both to patients with immediately life-threatening diseases (e.g., AIDS and certain uncontrollable cardiac arrhythmias) and to patients with other serious diseases (e.g., Alzheimer's and multiple sclerosis) for which no satisfactory alternative therapies exist. At least one new division will be formed in the drugs program and at least one new reviewing laboratory unit will be formed for biologics. Additionally, FDA will undertake new initiatives in the premarketing evaluation processes for foods and veterinary products.
3. **Postmarketing Surveillance.** FDA will continue to strengthen its postmarketing surveillance activities to enhance consumer protection against new and unforeseen risks with marketed products that do not become apparent through the analysis of small numbers of patients during the review process. Actions in the drugs and biologics area will include: expanding physician-based reporting; implementing routine electronic submissions of adverse drug reaction (ADR) periodic reports; evaluating the role of postmarketing surveillance in relation to new chemical entities; exploring alternative sample collection methods in the drug quality assurance surveillance program; and strengthening the drug product problem reporting program. Actions regarding medical devices will focus on development and implementation of a comprehensive strategy for utilizing the medical device reporting (MDR) system to assist in anticipating and resolving device problems. Actions in the foods area will include: postmarketing surveillance activities and

epidemiological studies that provide exposure and adverse reaction information regarding food ingredients; and further strengthening of the adverse reaction monitoring system (ARMS) for foods.

4. **Food Safety.** FDA will develop and implement an integrated set of initiatives to identify, prevent, and resolve existing and newly emerging public health problems in the nation's food supply. Particularly, the Center for Food Safety and Applied Nutrition (CFSAN) will maintain and enhance the science base which supports regulatory activities across the broad range of food safety concerns, work cooperatively with other Agency components to improve public education about food safety and nutrition, ensure the safety of imported foods, and enhance FDA's risk assessment capabilities.
5. **Veterinary Product Safety.** FDA will develop and implement an integrated program of initiatives and activities to identify, prevent, and resolve existing and emerging health problems related to the manufacturing, distribution, and use of animal drugs and feed additives. Specifically, the Center for Veterinary Medicine (CVM) will initiate efforts to improve and accelerate the new animal drug review process and will develop and implement compliance strategies, including development of model state codes and federal/state contracts to prevent the illegal sale, distribution, and use of animal drugs and feed additives. Furthermore, CVM will develop and implement an interagency tissue residue program to facilitate interactive enforcement activities based on carefully focused compliance/enforcement initiatives which are reinforced by an extensive intramural/extramural program of research to develop and validate new and/or improved methods for residue detection and quantification in animal-derived foodstuffs.
6. **Enforcement.** FDA will develop specific initiatives to improve its enforcement processes, to streamline its enforcement procedures, and to clarify its enforcement policies so as to provide more reasoned and uniform enforcement actions throughout the Agency. Special attention will be provided to enforcement activities involving complex or technical industry problems, deliberate criminal acts, and other violations, in order to provide more efficient processing of enforcement actions against deliberate violators.
7. **Imports.** Recognizing that substantially different conditions of food manufacturing and distributing exist around the globe, FDA will improve the coverage of imported products through improved intra- and inter-agency communications, increased use of automated programs, greater efforts to obtain more reasoned and uniform import enforcement actions throughout the Agency, and improved laboratories in the field to facilitate sample analyses. These efforts are needed to cope with the vastly increased number of imports and with major technological changes in manufacturing in the United States and abroad.
8. **Risk Assessment.** FDA will expand the risk assessment initiatives, begun during Action Plan Phase I, to improve the peer review/scientific base upon which risk assessments and consequently risk management decisions are made. FDA will develop and implement processes to insure that its uses of risk assessment techniques in carrying out its regulatory responsibilities contribute to promoting public health in a timely, effective, and efficient manner.
9. **Human Resources.** FDA will devise, develop, and where feasible, implement programs designed to more effectively recruit, develop, and retain its most valuable resource, its people. Particular emphasis will be directed at continuing the professionalism of the Agency; improving the management of the Agency's human resources and accountability thereof; and expanding the successful initiatives instituted under Action Plan Phase I through the Commissioner's Advancement Program (CAP).
10. **Information, Education, And Technical Assistance.** FDA will expand its use of information, education, and technical assistance to prevent or resolve public health problems amenable to these approaches. Special emphasis will be given to public education. Obvious examples of such efforts include but are not limited to the following: efforts to educate the public in recognizing and avoiding tampered-with products; education of health professionals in safe renal dialysis techniques; efforts to educate the agribusiness community on illegal drug residues in livestock; a joint effort with the states and the dairy industry to combat microbial contamination of milk and milk products; stepped-up efforts to network with the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency (EPA) in the area of chemical contamination of foods; increased efforts to network with local and state officials in the resolution of emergency and emergent health problems; and increased coordination with other organizations to combat health fraud.
11. **Commissioner's Special Initiatives.** Recognizing that, because of their broad-based organizational nature, the first ten goals do not address certain specific substantive areas of special concern, the Agency will undertake, under the leadership of the Commissioner, special initiatives for Women's Health, Science, Orphan Products, and Technology Assessment and Transfer—areas that the Commissioner has specifically selected for added focused effort.

APPII will be implemented under the immediate responsibility of Deputy Commissioner John A. Norris. The Action Plan Reporting and Evaluation System (APRES) will be the primary management tool for implementing, monitoring, and reporting. Objectives and milestones for each goal will be developed by the organization responsible for the goal after negotiations with the Deputy Commissioner and final approval of the Commissioner. Final objectives and milestones will be included in APRES, which will be maintained by FDA's Office of Planning and Evaluation.

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INTRODUCTION

An action plan is like a model of the future—it represents the best current estimate of future needs and directions, but since the current view of the future sharpens with the passage of time, the plan must be evolutionary, flexible, and designed so that implementation of the plan is the beginning of the action, not the end. The original charge to and commitment by Commissioner Young was to lead a planning process that will prepare FDA for the challenges of the 21st century. The accomplishments of FDA under Action Plan Phase I assured that major strides were made toward fulfilling that commitment. But the preparations are not complete. The Agency has embarked on a second phase of action planning. Action Plan Phase II (APPII) builds on the original planning process and the successful implementation of the July 1985 Action Plan. This document represents the best professional judgment of FDA and articulates a commitment to maximize FDA's effectiveness. FDA's efforts may need to deviate from this plan, however, because of competing priorities and the availability of resources.

DEVELOPMENT OF APPII

The process of developing APPII was initiated by Commissioner Young on July 30, 1986 through a memorandum which outlined the scope of the process. Specifically, the Commissioner charged the Deputy Commissioner, the Center Directors, and the Associate Commissioners to develop candidate APPII initiatives. Commissioner Young also specified three selection criteria that should in all cases be applied to candidate initiatives. In summary, it provided that APPII initiatives must be seen by the Agency's constituencies and employees as:

a. Contributing to the public's health,
b. Being within the Agency's area of responsibility, and
c. Representing a cost effective expenditure of scarce Agency resources.

The Commissioner, in the July 30 memorandum, listed areas of special interest that should be considered during the development of APPII. These special interest areas included: new product review processes; food safety; veterinary medicines; the scientific capacity of the Agency; risk management; risk assessment; and public health issues of particular concern to women. The APPII process is both a top down and participative bottom up planning effort. It taps both the strategic expertise of the Agency's top management and the specific initiative developing expertise of the Agency's line management.

As a result of the Commissioner's call, Agency organizations in October suggested more than 40 initiatives for APPII. These initiatives were analyzed by the planning staff and recommended to the Commissioner by Policy Board members and deputies. To begin the necessary focusing of these initiatives into more forward looking goals for APPII, the results were discussed in an evening session in November. One major result of the November Policy Board discussion was the emergence of a clear consensus that APPII should reflect three major areas for action: ***Health Problem Identification, Health Problem Prevention,*** and ***Health Problem Resolution.***

1. ***Health problem identification*** (including quantification) is a necessary first step in protecting the public health. Problems must be recognized, quantified, and clearly delineated so that mechanisms and processes can be developed and/or implemented to prevent or resolve the problem. Examples of FDA's identification processes include: postmarketing surveillance activities; postmarketing studies; risk-assessments; clinical reviews; product inspections; and ongoing regular communications between FDA and consumers, health care providers, industry, and their respective representatives.
2. *Health problem prevention* efforts focus on joint efforts of government, industry, health professionals, and consumers to keep identified potential problems from occurring or recurring. Government has a necessary role in informing manufacturers about products they make and consumers about products they use (so that they can make informed decisions). While the first line of defense in protection is individual responsibility, government serves by protecting consumers from risks beyond their capabilities of self-protection. Industry has the responsibility to assure to the best of their ability that known risks that are reasonably preventable are not present in their products and that other known risks are told to consumers and are reasonably minimized. Health professionals serve an important role in informing the consumer. Examples of FDA's prevention processes include:

premarket product reviews; guidelines on policy issues; regulations on harmful substances (e.g., sulfites); informative labelling (e.g., OTC drug products, salt, cholesterol); and education programs.

3. *Health problem resolution* is a parallel effort to protect the consumer by capping, reducing, or eliminating identified problems. A wide variety of methods are used to resolve health problems, including: research; education; regulations; enforcement actions leading to voluntary compliance; seizures, injunctions, and criminal prosecutions; and public information campaigns. Of particular note are the widespread and effective results of networking between FDA and state and local health officials, as exemplified by FDA's actions in the recent product tampering incidents.

Following the November Policy Board meeting, using the guidance developed at that time, a series of major initiatives were identified as necessary to address concerns in these three areas. In December the Policy Board members and their deputies again met to discuss the draft versions of these initiatives. Out of this consensus process and with a strong sense of commitment, the Agency's top management dedicated its future efforts to accomplishing a second phase of the Action Plan.

AN ELEVEN POINT PLAN OF ACTION

Based on the Commissioner's three criteria (public health contributing, Agency responsibility, and cost effective) and within the three overall priority areas of emphasis (problem identification, prevention, and resolution) FDA is hereby establishing an 11-point program for APPII to fully meet the most urgent needs facing the Agency and the public. These eleven key initiatives include:

1. **Acquired Immunodeficiency Syndrome (AIDS)**
2. **Premarketing Product Evaluation**
3. **Postmarketing Surveillance**
4. **Food Safety**
5. **Veterinary Product Safety**
6. **Enforcement**
7. **Imports**
8. **Risk Assessment**
9. **Human Resources**
10. **Information, Education, And Technical Assistance**
11. **Commissioner's Special Initiatives.**

The following sections of this plan provide specific details on the elements of each of these goals. Particular reference should be made to goals 4 and 5 for an illustration of how two program goals (food safety and veterinary product safety) integrate initiatives in health problem identification, health problem prevention, and health problem resolution.

IMPLEMENTATION

APPII will be implemented in much the same manner as Action Plan Phase I, with the Deputy Commissioner again having overall responsibility for the Plan's implementation. The Action Plan Reporting and Evaluation System (APRES) will be the primary management tool for implementing, monitoring, and reporting. Objectives and milestones for each goal will be developed by the organization responsible for the goal after negotiations with the Deputy Commissioner and final approval of the Commissioner. Final objectives and milestones will be included in APRES, which will again be maintained by FDA's Office of Planning and Evaluation.

1. ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

FDA will place special emphasis on producing the most timely, effective, and efficient research and premarketing review possible of products that offer promise for treating, curing, or preventing AIDS or AIDS-related diseases. Particular emphasis will be given to advising sponsors on the regulatory process, to upgrading productivity by focusing on rate-limiting steps in the review process, and to conducting research that will contribute to enhancing the product review processes both for drugs and for vaccines.

AIDS is an explosive public health problem. Close to 33,000 Americans have contracted AIDS; over half are now dead, and no one is known to have recovered from the disease. An estimated 1 million to 1.5 million individuals are infected with the AIDS virus; the number of these who will develop AIDS is unknown. By the end of 1991 it is projected that a cumulative total of 270,000 cases of AIDS will have been reported in the United States, with a projected total of 179,000 deaths. AIDS demands FDA's highest commitment to be responsive to the public's needs.

The conquest of AIDS has been identified as the President's number one public health priority. FDA's role in the PHS activities concerning the AIDS epidemic is based on FDA's responsibility to oversee approval of safe and effective drugs, biologicals including vaccines, and devices used in the care and treatment of AIDS patients. FDA is responsible for the safety of the blood supply through licensure of blood and plasma collecting facilities, development of regulations for the manufacturers of blood products, and licensure of the products themselves. FDA is also responsible for monitoring the use of investigational new drugs, including therapeutic substances and vaccines in humans, and for approving and/or licensing these products for marketing. Furthermore, FDA research scientists have joined with others throughout the biomedical scientific community in a massive research effort to identify therapeutic modalities to treat (and to develop a vaccine to prevent) AIDS and AIDS-related diseases. Particularly important in these efforts are conferences with sponsors prior to filing IND applications.

FDA is playing a major role in the federal government's response to AIDS health care delivery issues by participating in the Intragovernmental Task Force on AIDS Health Care Delivery. Through participation on the PHS AIDS Executive Task Force, FDA is playing a major role in PHS's initiatives. Under the overall guidance of the PHS Executive Task Force, committees were established at NIH and FDA to deal with AIDS initiatives in three major areas: prevention (including vaccine development and public education), therapeutic intervention, and blood safety. Coordination of the screening and clinical testing of products identified as potentially useful for treatment of AIDS has been achieved through close interaction between these groups at the working staff level. This coalition of talent and interagency dialogue will help to ensure the application of new AIDS therapies in patients as promptly as is scientifically and ethically appropriate. Further, it will provide an efficient mechanism for the sharing of results with non-AIDS specialists within the medical community and with the general public.

PHS's role in keeping the public informed has been of the utmost importance to public health because of the many misconceptions prevalent about AIDS. With respect to specific areas under FDA's jurisdiction, the Agency has worked with NIH and the Centers for Disease Control (CDC) to disseminate information on topics that are rapidly developing or changing.

FDA and NIH also work together closely to facilitate the development and evaluation of any therapeutic or preventative agent which appears to be promising. This integration of FDA into the total AIDS effort guarantees that, as was the case with the Human T-cell Lymphotropic Virus-Type III (HTLV-III) antibody test, any promising product will get expedited regulatory review and become generally available in the shortest possible time.

FDA's efforts in this process are of two sorts: (1) review of data submitted in support of applications for investigations of experimental products, or for applications requesting permission to market such products; and (2) research targeted toward resolution of specific problems that might hinder an experimental product's development and approval. Products included in this process are therapeutic agents directed against the AIDS virus itself and/or the opportunistic infections associated with the disease, products which might repair the immunologic deficits seen in the disease, and products for immunizing against the AIDS virus.

The Center for Drugs and Biologics (CDB), at a minimum, will take a number of specific actions to: assure highest priority is given to applications for products that will treat, cure, or prevent AIDS and AIDS-related diseases; and to give high priority to AIDS research. These actions will include the following specific initiatives:

Expeditious Review of Applications

CDB will expeditiously process all investigational new drug applications (INDs), new drug applications (NDAs), and applications for licensing of AIDS products or vaccines.

CDB has assigned all potential AIDS therapies a 1-AA designation—the absolute highest priority in the drug review process—and will take all measures necessary to assure prompt administrative processing and scientific review of AIDS related submissions.

Similarly, CDB will give top priority attention to immunizing agents. These submissions will be designated "AIDS priority" which shall have the same effect as designating them 1-AA within the resource constraints of CDB.

In either system these top priority designations will mean:

a. Special pre-IND consultation to expedite getting the drug into initial clinical (human) studies;
b. Expedited determination of orphan drug status; and
c. Expedited review of AIDS therapies for final commercial marketing approval, with completion in less than 180 days of FDA review time, and similarly expedited review of preventative agents, such as vaccines, globulins, and other biological products.

CDB has reallocated available resources toward facilitating development and approval of promising AIDS therapies. Despite these reallocations, there is significant concern both within FDA and in other PHS agencies that the level of future effort required is certain to outpace these additional resources, particularly in the burgeoning AIDS vaccine development area. Thus CDB will put additional resources into this task by the formation of one or more additional laboratory based units staffed with regulatory reviewers/researchers, and will seek additional laboratory facilities.

Blood Test Research and Development

CDB will improve blood testing strategies for detecting AIDS virus(es) and will develop more sophisticated methods for handling blood donors with antibodies to the AIDS virus(es).

The risk of transmission of HTLV/LAV by transfusion of blood has been greatly reduced. Serologic tests to detect HTLV-III antibodies have been licensed and the tests are being used to screen donated blood and plasma. Antibodies do not form immediately after exposure to the virus. Therefore, a newly infected person may unknowingly donate blood which contains HTLV-III and escape detection if detectable antibodies are not yet present in the blood. CDB will continue the search for more effective blood tests capable of enhancing FDA's ability to assure the safety of the nation's blood supply.

Vaccine Product Research

CDB will address the considerable concern within PHS that every effort be put forth to respond appropriately to the need to expeditiously develop and test AIDS vaccines. The key to enhancing the effectiveness of FDA's role in facilitating vaccine development is to expand the already functioning partnership between the regulatory scientists/reviewers in FDA and their counterparts from outside organizations engaged in vaccine development, by adding additional personnel as noted in the preceding section. These additional laboratory unit(s), at a minimum, will add to CDB's capability to timely, effectively, and efficiently assess the vaccines composition and the production and laboratory testing methods used. it will allow the evaluation of improved methods of preclinical testing, including the use of animal models, and will allow CDB to assist in the clinical evaluation of the wide variety of experimental products that are currently under development. There is also a need to expand in-house studies on the characteristics of the retroviruses generally and to define their importance for humans. It will be important for FDA to have the capability to deal with these viruses, since it is highly likely that the Agency will be confronted with an increasing number of products related to them.

Contract Research

CDB will develop a plan for more effectively contracting for AIDS research. Contracts for the more promising projects will be awarded expeditiously. CDB also seeks contractors who are able to conduct basic research on issues raised by the AIDS epidemic. Several laboratory groups have conducted research concerning the basic immunologic defects associated with the disease (which might contribute to understanding how biologic or drug products might combat the virus). Additionally, there are FDA contract research studies of characteristics of the family of retroviruses (see preceeding section) that might be important in developing vaccines and therapeutic agents.

These initiatives represent FDA's continued commitment to *aid in the conquest of AIDS by providing the most timely, effective, and efficient research and premarketing review possible of products that offer promise for treating, curing, or preventing AIDS or AIDS-related diseases.*

2. PREMARKETING PRODUCT EVALUATION

FDA will increase its efforts in improving premarketing evaluation processes for drugs and devices, begun during Action Plan Phase I. Particular emphasis will be given to the recruitment and training of personnel for the reviewing divisions and on methods to enhance retention of existing review personnel. Recognizing the importance of scientific research in the reviewing divisions, FDA will enhance its scientific expertise in biologics, devices and drugs.

Timely, effective, and efficient evaluation of products requiring FDA's approval prior to being marketed is an important and highly visible responsibility of the Agency. The Agency thus plays a dominant role in technology transfer through its premarketing review process.

Major attention and redirection of resources went into making significant improvements in the product evaluation process for drugs and devices during the initial implementation of the Action Plan. Yet much remains to be done. The importance of this activity requires continued efforts to further improve these and the other product evaluation processes. The review of food and color additive petitions is receiving renewed attention but in this plan is discussed separately under the food safety initiatives (See Goal 4, Food Safety). Likewise the review of new animal drugs is discussed in the section on veterinary drugs (See Goal 5, Veterinary Product Safety). This section of Action Plan Phase II (APPII) describes the initiatives to be undertaken in the human drugs and new medical devices product areas as well as the cross-cutting activities under the patent term restoration initiative.

HUMAN DRUGS

Action Plan Phase I focused attention on a number of activities designed to improve the timeliness, effectiveness, and efficiency of the new drug review process as its highest priority. The Agency's commitment remains steadfast and improving new drugs and biologics product review is the highest Agency priority. Significant improvements occurred as a result of this focusing of attention during Action Plan Phase I. Several significant activities begun during Action Plan Phase I are among the approximately 15% of milestones (contracts) not yet due for completion and will be continued and completed under APPII. Additionally, significant new initiatives will be undertaken under APPII. The following describes CDB's significant Phase I accomplishments, their continuing activities, and their new initiatives for APPII.

IMPROVEMENTS UNDER ACTION PLAN PHASE I

Under Action Plan Phase I, significant accomplishments that improved the timeliness, effectiveness, and efficiency of the new drug review process included:

a. Delegating certain sign-off authorities from office level to review division level. This new delegation authorized the six division directors to approve applications for new salts, some new formulations, and certain new indications for approved drugs. The six new drug division directors now complete the review of about 50% of all new drug applications without subsequent review by upper management;
b. Assigning all potential AIDS therapies its top priority—a 1-AA designation—during both the investigational new drug (IND) and new drug application (NDA) stages. The first application of the new 1-AA designation was to the drug azidothymidine (AZT). Preclinical studies conducted in CDB's Division of Virology Labs and the National Cancer Institute were among the first to indicate AZT's inhibitory effects on the HTLV-III virus, the agent which causes AIDS. In 1985, FDA approved the first clinical (human) testing of AZT within five days of receiving the application. When early clinical tests proved promising, FDA approved the expansion of clinical trials, which led, ultimately, in late September 1986, to FDA approval of a treatment protocol (treatment IND) in seven days;
c. Expediting completion of action on NDA efficacy supplements. This effort resulted in a 33% reduction in the number of overdue efficacy supplements in about nine months;
d. Completing new guidelines implementing the NDA rewrite. The new regulations designed to streamline the NDA process became fully effective in May 1986. In order to help companies prepare NDA's in a more uniform and efficient format, a series of guidelines were prepared. A public workshop to discuss these new guidelines was held in the spring of 1986;

e. Implementing improvements in the IND and NDA management information systems, developing staff training programs, and eliminating redundant reports and reviews. These steps combined to free up more time for reviewing applications by the reviewers, to help reviewers and supervisors keep better track of all aspects of an application's status in the review process, and to help all staff keep their skills sharpened;

f. Improving the number and variety of significant products derived through biotechnology, approving a record number in fiscal year 1986. In June 1986, FDA licensed preparations of interferon to treat a rare adult leukemia—hairy cell leukemia—for which there had been no effective therapy. Also in June, FDA approved the first therapeutic use for a monoclonal antibody within the human body to reverse acute kidney transplant rejections. Called Orthoclone (OKT*3), this pioneer drug is produced by fusing one antibody producing cell with an ever-reproducing cell, resulting in a hybridoma producing a specific and uniform antibody. A third biotechnology milestone was achieved in July 1986 when FDA licensed a genetically engineered vaccine for the prevention of hepatitis B, one of the most serious forms of viral hepatitis; and

g. Implementing Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act). Six months ahead of schedule, CDB met the commitment to complete the initial review of applications within the statutory limits. Simultaneously, CDB met in a timely fashion all other objectives mandated by this new law and by Agency management. Listings of approved products, patents, and exclusivity determinations were developed and published. A new Division of Bioequivalence was organized and staffed. New policies and guidances were written and communicated to industry through letters, journal articles, and seminars. A fast response system was initiated to process petitions for abbreviated new drug application (ANDA) eligibility, which expedites the flow of new innovations to the marketplace, and eliminates the need for superfluous studies, but preserves FDA's traditionally high standard of scientific decision making. A public hearing was organized to solicit input on procedures used by FDA to establish bioequivalence. The hearing was chaired by FDA's Commissioner and Deputy Commissioner and attracted more than 800 participants.

   The Hatch-Waxman Act came to FDA with the resources that the Commissioner had determined to be necessary for its implementation. The implementation itself showed the remarkable ability of FDA to assimilate these new resources and live up to the expectations of the Administration and Congress.

These accomplishments received recognition and awards from the Congressional sponsors of the legislation, the Administration, and consumer and industry groups.

CONTINUATIONS FROM ACTION PLAN PHASE I

Computer-Assisted NDAs

CDB will: (a) continue to explore whether and how a variety of uses of automated data systems can enhance the timeliness, effectiveness, and efficiency of the drug review process and reduce burdensome nonessential hard-copy data handling; (b) complete currently ongoing experiments involving use of automated submissions of NDA data; (c) evaluate these experiments and look for opportunities to initiate new experiments; and (d) investigate new approaches to performing biostatistical reviews of NDAs. Since clinical and biostatistical sections of NDAs are closely related, any improvements achieved in the latter should assist the performance of NDA clinical reviews. New models will be developed and used for explaining how to conduct a review of the biostatistical sections. Formats for the submission of data will be designed and shared with sponsors and applicants. These will include illustrative examples of information that is pertinent to validating biostatistical analyses of data from clinical trials.

IND Rewrite

INDs are the starting point for the process that may result in approval for marketing of a new drug entity. The initial phase of the IND process focuses on innovation whereas the latter phase focuses on verification. In March 1987, FDA reproposed procedures to make investigational new drugs available to desperately ill patients before general marketing begins. These procedures are intended to facilitate the availability of promising new drugs to patients as early in the drug development process as possible, and would apply to patients with immediately life-threating or other serious diseases for which no satisfactory alternative therapies exist. The procedures for immediately life-threatening diseases would apply, for example, to advanced cases of AIDS and certain uncontrollable cardiac arrhythmias, while the procedures for other serious diseases would apply, for example, to Alzheimer's and multiple sclerosis.

Effectiveness Supplements

Effectiveness supplements to NDAs cover such potentially important expansions of the NDA as new indications for use, new dosing regimens, and new routes of administration for approved drugs. Under Action Plan Phase I, CDB established a system for monitoring the processing and review of these supplements, inventoried them, and developed a system to assign priorities for review. The result was a substantial reduction (in excess of 30%) in the backlog of overdue applications. CDB will consolidate these advances and extend progress by ultimately eliminating the backlog of overdue NDA effectiveness supplements.

Guidelines

CDB will complete and publish notices of availability of the remaining format, content, and substantive NDA and Drug Master File guidelines.

Generic Drugs

CDB will continue to expedite the review of generic drugs. Even though applications are now threefold over levels prior to the Hatch-Waxman Act and the workload has consistently increased, 90% of all initial reviews will be completed within 160 days of filing. By September 30, 1987, CDB will develop plans for accommodating the long term, the vastly expanded ANDA files. A special task group will review the 800 page transcript of the Bioequivalence Hearing plus all the comments to the public docket and will publish its recommendations by October 31, 1987. The program of information and education to the industry regarding implementation of the Hatch-Waxman Act will continue.

NEW INITIATIVES FOR ACTION PLAN PHASE II

IND/NDA and Biologics Licensing Review

CDB will launch additional initiatives to facilitate further improvements in the quality, efficiency, and timeliness of the review process. These improvements will substantially reduce the length of time to complete reviews, substantially reduce the number of overdue NDAs, and eliminate overdue supplements. The public benefits directly from earlier availability of improved and diversified therapies. A second more indirect public benefit results from the financial gains to sponsoring companies from earlier approvals which in turn provide impetus to research and development funding and incentives for future new chemical entities (NCEs). Three years after the recruitment of the required staff, obtained from a combination of reallocation of resources and new resources, the Agency should be able to complete reviews in an average of 12 months, as compared to the current average review time of 27 months. To this end, CDB will carry out organizational "fine tuning", and provide additional application guidance for sponsors, applicants, and staff; carry out additional experiments involving automation of NDA data and reviews; undertake innovative programs for recruitment, orientation, and training of scientific staff; and improve library services that directly support the drug application review process. These steps will eliminate the "dead" time (i.e., time spent waiting in queue for reviewer action) and will substantially reduce the "decision" time (i.e., the length of time spent to reach a decision on the approval or non-approval of the application). Additionally, FDA will develop new policy for making promising new drugs available to patients as early in the drug development process as possible, where no satisfactory alternative therapies exist. Specifically, with respect to IND and NDA review, CDB, at a minimum, will:

a. Develop procedures for dealing with requests for treatment protocols under the revised IND regulations;
b. Eliminate the backlog of overdue NDA effectiveness supplements and substantially reduce the queues of applications of all types awaiting review;
c. Substantially reduce the total number of overdue NDAs and the average review times for NDAs;
d. Complete the design and receive Agency approval of a plan for establishment of at least one new drug review division, which should assure a more balanced workload;
e. Identify other significant bottlenecks at all levels of the review process and take appropriate measures designed to widen or remove them;
f. Design and implement new organizational approaches to facilitate the review of products that cut across organizational lines;
g. Develop and provide to the drug review divisions guidance on how to make final review decisions (rather than deferring final action by means of requesting additional information from the applicant) when data are found to be insufficient for approval. This allows definitive action to be taken more efficiently and expeditiously;
h. Sponsor seminars and meetings directed toward informing drug application submitters about what CDB needs and expects in reviewing submissions. Improved submissions will facilitate improved and efficient review;
i. Install the equipment necessary to utilize new automated formats to improve the timeliness, quality, and efficiency of reviews of biopharmaceutical sections of NDAs; and
j. In biologics, CDB will develop a program to support the National Vaccine Program with particular emphasis on biotechnology.

Reviewer Recruitment and Training

The Agency's ability to maintain and improve the quality of drug application reviews is dependent on the recruitment and retention of additional highly qualified scientific reviewers. Equally true, much of the delay in drug review is produced by the lack of enough qualified scientific reviewers to handle the heavy review workloads, leading to long queues at various stages, which FDA is committed to substantially reduce. To that end, there is a clear need to retain qualified staff who are fully conversant with up-to-date technology and who are experts in the evaluation of the various types of data found in drug applications. Also, there must be new staff recruited and oriented to the unique duties they will fill. CDB is implementing an extensive program, using innovative approaches, to recruit scientific reviewers, particularly medical officers. This program is being undertaken in collaboration with the Pharmaceutical Manufacturers Association (PMA), the

American Medical Association (AMA), and the Institute of Medicine (IOM). Through three separate task forces, FDA is: studying ways of increasing the effectiveness of the FDA recruitment program for medical officer reviewers; exploring the development of a Distinguished Fellow Program; and developing a structured multi-year university-affiliated fellowship training program designed to augment medical officer review staff.

CDB will also seek to work with other institutions, as it already is with the Children's National Medical Center, to develop a variety of fellowship programs that will offer a range of opportunities to work at, and learn at, FDA. Finally, increased attention will be directed to devising training and orientation programs both for new and for existing review staff members.

Library Support to the Drug Review Process

CDB operates a medical library which is extensively used by drug application reviewers. The library maintains an extensive collection of books and journals, has access to selected on-line bibliographic retrieval services, and can perform scientific literature research services upon request. CDB will improve library services in several areas as follows:

a. Strengthen the collection of reference materials and files that directly support drug review;
b. Develop an automated integrated library system which will include an online catalog and listings of reports and periodicals and online access to reviewers from their work areas; and
c. Provide a central repository for IND/NDA guidelines in the form of an indexed, full-text database.

OTC Review

CDB will continue to increase its efforts to complete the review of over-the-counter (OTC) drug products. In 1986 FDA issued a final rule providing manufacturers with flexibility in labeling language used to describe the intended use of an OTC product. Previously, the Agency's "exclusivity" policy permitted only official language, approved by FDA, to be used on an OTC drug label. The new rule frees manufacturers to use their own words to describe an OTC drug's intended use, so long as the alternative wording is truthful and not misleading. FDA views this action as accelerating the pace of OTC monograph development. Building on this successful accomplishment CDB intends to take additional steps under APPII to expedite the publication of OTC monographs. Specifically, within the next 12 months the Agency, at a minimum, will publish proposed rules for the following four categories of drugs:

1. Internal analgesics;
2. Cough and cold combinations;
3. Anti-fungal products; and
4. First aid and hospital use antiseptics.

In addition FDA will explore a number of new means to enhance the consumer use of OTC medications.

NEW MEDICAL DEVICES

The Center for Devices and Radiological Health (CDRH) has made significant progress in improving its implementation of the Medical Device Amendments of 1976. There is, however, a need for continued improvement in the new product review process. Rapidly expanding technology has created a rise in the number and complexity of medical devices, requiring an increasingly sophisticated level of scientific review. CDRH will continue to streamline the product review process and make it more efficient. This and close husbanding of resources is needed to cope with the workload and limited resources.

At the same time, CDRH will be mindful of the necessary balance among fully and aggressively safeguarding the public health, streamlining the process, not stifling product innovation, and not placing undue economic burdens on industry.

IMPROVEMENTS UNDER ACTION PLAN PHASE I

Under Action Plan Phase I, several initiatives were undertaken to improve the product approval process including:

a. Publishing a final regulation and guidance document which provided to the medical device industry clear and uniform procedures for developing premarketing approval applications (PMAs). This effort should result in the submission of better organized and more complete applications, requiring less review time and fewer subsequent requests for data from manufacturers;
b. Publishing a guidance document on its premarketing notification [510(k)] review program which will clearly delineate the aims of the 510(k) program and the types of information required in applications. This effort is designed to improve the quality of 510(k) submissions and should thus result in more uniform and consistent premarketing notification reviews;
c. Developing 510(k) exemption criteria, which will eliminate unnecessary premarketing notifications for certain medical devices and is projected to reduce unnecessary applications by more than a thousand over a three year period;
d. Allowing the addition of new institutions and investigators to conduct studies on investigational devices without prior FDA approval, which is estimated to reduce unnecessary submissions by more than a thousand per year;
e. Placing on applicants for premarketing review of new devices the initial responsibility for preparing drafts of the safety and effectiveness summaries (that would ordinarily be wholly prepared by FDA), which is expected to shorten review time by a full month for each device; and
f. Developing and implementing a computerized tracking system which is used to identify overdue applications and provide other performance data to help manage the timely, effective, and efficient review of product approval submissions.

Significant progress was made in enhancing the timeliness and productivity of the new product review process while also increasing its quality. For example, in FY 86, CDRH approved a *record 72 original* PMAs, compared to 37 such approvals in FY 85. CDRH also approved a *record number of PMA supplements, 477*, which compares favorably to the previous record of 377 approved in FY 85. For investigational device exemption (IDE) applications, review time was reduced from an average of 37 days in FY 85 to 28 days in FY 86. For IDE supplements, average review times dropped from 33 days in FY 85 to 21 days in FY 86.

CDRH will undertake to further improve the quality, timeliness, and efficiency of the product review process through a variety of continuing and new activities, which are designed to further reduce review times for premarketing approval applications; to provide a better, more reasoned, and consistent review; and ultimately to reduce the backlog of applications awaiting review. These steps will eliminate the "dead" time and will substantially reduce the "decision" time.

ACTION PLAN PHASE II INITIATIVES

Investigational Device Exemptions

CDRH will develop an investigational device exemption (IDE) expansion policy which will specify criteria for increasing the use of medical devices during an investigation, thereby making new technologies and treatments available to those who need them while at the same time (1) allowing manufacturers to gather the necessary clinical data to support the safety and effectiveness of their medical devices, and (2) protecting the public more generally from unproven, though promising, medical devices.

Clarifying Reclassification Policy

CDRH will develop a policy clarifying reclassification requirements. Such a policy will provide for the downclassification of technologies for which experience has shown that the higher classification is no longer necessary to protect the public health. Thus the Agency will enhance consumer safety by attention on those devices that pose a genuine threat to public health rather than toward mechanical regulatory requirements with little payoff in terms of public health benefits. This will also eliminate unnecessarily burdensome regulatory controls for industry, lower the cost to industry of complying. Additionally, it will minimize unnecessary economic barriers to industry entry into the marketplace, particularly important for small manufacturers (the predominant size of medical device manufacturers), thereby enhancing technology transfer.

Guidance for 510(k)s

The premarketing notification [section 510(k)] process allows a company to market a medical device, without submitting a PMA, if the device is substantially equivalent to a device that was marketed prior to enactment of the 1976 amendments. To clarify responsibilities, CDRH will develop a 510(k) modification guidance document delineating manufacturers' responsibilities for validating changes to a marketed device and FDA's responsibilities in reviewing these changes in the 510(k) process.

510(k) Exemptions

CDRH will continue to apply its 510(k) exemption criteria to appropriate products in order to concentrate on significant public health issues and to reduce unnecessary submissions that have little public health value.

Recruitment and Retention of Reviewers

CDRH will develop new initiatives designed both to improve the recruitment and training of new reviewers and to increase the retention of current reviewers through making better career opportunities at FDA available to them.

Transitional Products

The Agency will continue its focus on solutions aimed at improving the efficiency and effectiveness of the product review process (e.g., classifying transitional products regulated as new drugs prior to the 1976 Amendments). Transitional products, automatically in Class III, account for 15% of CDRH's product review workload. For example, classification of these products into a more appropriate regulatory class based on estimates of risk will free up resources for those products which present greater risk to the public health, thereby reducing unnecessary regulation and enhancing necessary regulation.

Automated Tracking Systems

CDRH will continue to improve its automated tracking systems for 510(k)s, IDEs, and PMAs, which will further enhance it's capability for tracking and processing documents. CDRH will also initiate development of an integrated center-wide data base.

Electronic Transmittals

CDRH is also developing a capability for electronic transmission of data by manufacturers in support of applications. During 1986, a number of test transmissions were conducted with several manufacturers. As a result, CDRH has developed a draft protocol for use in transmitting documents. This protocol is currently under review in the Agency. Implementation of the final protocol will further streamline the application review process.

PATENT TERM RESTORATION

The successful completion of the initiatives in Action Plan Phase I established a promising beginning for the Agency's implementation of the patent extension provisions of the

Drug Price Competition and Patent Term Restoration Act of 1984. The Office of Health Affairs (OHA) exceeded its Action Plan Phase I commitment by completing first 90%, and more recently 95%, of FDA's regulatory review period determinations within the statutory limit of 30 days after receiving a patent extension application from the U.S. Patent Office. This high level of statutory compliance is remarkable in light of the novelty of FDA's involvement with the patent laws and the brevity of the statutory timeframe for action. OHA also developed and published proposed regulations implementing FDA's patent term restoration duties under the new law. In the process of completing its Action Plan Phase I milestones (contracts), OHA established a strongly cooperative working relationship between FDA and the Patent Office.

OHA will undertake at least two new patent term restoration initiatives under APPII. These include:

Development and Agency Clearance of the Final Rule Governing FDA's Patent Term Restoration Duties

FDA's final rule on its patent restoration duties and the Patent Office's regulations governing that agency's functions under the new law will complement one another and together will define the regulatory environment for patent extensions. The Patent Office's proposed regulations are proceeding in parallel to FDA's regulations, benefiting from the dialogue now well established between the two sister agencies.

Development of Programs to Foster Innovation

OHA will develop programs to foster innovation in human drugs, medical devices, and food and color additives by raising awareness of the patent extension program within FDA and among industry members, researchers, and the public.

The initiatives undertaken by FDA under APPII will make *major contributions to the public health and will result in significantly enhanced processes for the premarketing evaluation of drugs, biologics, and medical devices.*

3. POSTMARKETING SURVEILLANCE

FDA will continue to strengthen its postmarketing surveillance activities to enhance consumer protection against new and unforeseen risks with marketed products that do not become apparent through the analysis of small numbers of patients during the review process.

It is recognized that premarketing testing is extensive and FDA's review of test data are the most thorough in the world. But even under the best of circumstances premarketing review cannot provide complete assurance or information on the product for its use in larger sizes and differing types of population. FDA's responsibilities cannot and do not end when a product is commercially marketed.

Figure 1 depicts the sequence of drug development, FDA premarketing review, and FDA postmarketing review as a single, fully integrated system. The Agency is charged with assuring that the product is safe in actual use by the larger more diversified population. Postmarketing surveillance is the monitoring and assessment of product performance after approval for commercial introduction into the market and is a vitally important—and fully integrated—part of FDA's new product review process. It provides information that leads to the enlargement of the sponsor's claims or narrows the indication of use—sometimes even to the extent of a market withdrawal. Because of the relatively small number of human subjects generally, that reasonably and ethically can be studied prior to approval of a product, ongoing postmarketing surveillance is an essential part of the overall review process.

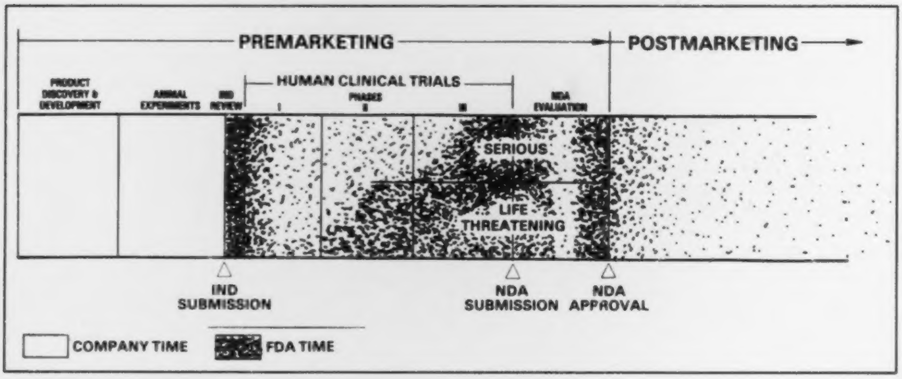
Action Plan Phase I placed high priority on strengthening postmarketing surveillance activities in the drugs area. Action Plan Phase II (APPII) continues this high priority attention to drugs and includes new emphases on strengthening postmarketing surveillance activities in the medical devices, foods, and veterinary products areas.

HUMAN DRUGS

A patient's health and response to therapy depends upon both his or her and the health care provider's full knowledge both of the beneficial and of the toxic effects of drugs. Human drugs undergo extensive and costly testing and review prior to approval, but premarketing testing cannot provide complete assurance or information on their safety and effectiveness. This is mainly because of the practical

Figure 1

NEW DRUG DEVELOPMENT AND REVIEW PROCESS



limitations on the size and types of populations studied in the conduct of human trials. The role of postmarketing surveillance (PMS) is to provide additional safety information that cannot realistically be developed before drug approval, primarily in the first three years after approval of a new drug. Once the actual risks are identified through careful PMS studies, both patients and care providers can be informed so that drugs can be judiciously and appropriately used, following informed balancing of benefits against risks.

One key to conducting useful surveillance is the maintenance of a system for adverse drug reaction (ADR) reporting. Analyses of the ADR reporting system have shown that, with proper input from the health professional community and strong management from FDA, it can generate effective postmarketing signals of a drug's beneficial and toxic effects.

CDB will build on the experiences gained and successes achieved under Action Plan Phase I and will undertake the following APPII initiatives:

Physician-Based Reporting

As one initiative of Action Plan Phase I, FDA previously contracted with three states (Rhode Island, Maryland, and Mississippi) to study physician-based reporting of adverse drug reactions. These contracts are aimed at improving direct physician reporting. Historically only about 10% of reports come directly to FDA from physicians and other health providers. Since reports from physicians generally contain a higher proportion of both serious and effectively described reactions than those received from industry, FDA's encouragement of increased reporting from physicians is expected to significantly enhance the usefulness of the ADR system. Under APPII the Center for Drugs and Biologics (CDB) plans to extend by one year, one or more of the three current state contracts to further evaluate the impact of State health department interventions on the quantity and quality of physician-based adverse reaction reports. The data received from the States will be evaluated and summarized. If the pilot projects are successful, sentinel reporting areas may be established. The sentinel reporting areas would be select states where special attention is given to direct physician reporting.

Computerized Tape Submissions

Under APPII, CDB will develop and test means for industry to provide electronic submission of ADR periodic reports. An Action Plan Phase I pilot study tested the feasibility of the submission of periodic ADR reports to FDA by electronic means (e.g., by modem or on computer tapes or floppy disks). Based on the encouraging findings of the pilot test, an operational procedure for submission of periodic reports on floppy disk is being finalized. CDB plans to make available to industry one or more additional procedures for submitting periodic ADR reports by electronic media. CDB will assess the need and feasibility of new regulations or guidelines which would assist industry in providing these electronic data submissions. These changes are expected to increase FDA's capacity to receive and use ADR reports as a tool for postmarketing assessment of drug safety by facilitating internal processing, improving accuracy, and thereby improving the timeliness of ADR reports.

ADR Reporting Requirements for Drugs Without Approved NDAs

The Final Rule covering ADR reporting requirements for all prescription drugs was published in the July 3, 1986, *Federal Register* and became effective on September 2, 1986. Previously, sponsors of drugs marketed prior to the requirements for filing an NDA or an ANDA did not have to report adverse reactions to the drug product. This rule provides consumers with the same level of protection against serious, unexpected ADRs for all human drugs, regardless of NDA status.

ADR Reporting Requirements for Biologics

Under Action Plan Phase I, draft reporting requirements for adverse reactions to biological products were developed. The purpose of this reporting requirement was to make biologic product ADR reporting consistent with what is required for drugs. CDB intends to publish and revise as appropriate a Proposed Rule for these new reporting requirements under APPII.

New Surveillance Activities

Two new surveillance objectives will be initiated under APPII:

1. The existing research program in pharmacoepidemiology will be reviewed to determine if redirection is necessary. If redirection is deemed appropriate, priorities for research will be established and new requests for proposals for conducting the research will be initiated; and
2. The role of postmarketing surveillance in relation to selected previously approved new chemical entities (NCEs) will be evaluated to determine whether, in addition, postmarketing studies for safety problems would have been appropriate. For NCEs where postmarketing studies may be needed, an evaluation of the study needed will be conducted. CDB will then develop criteria and a plan for initiating early postmarketing studies on selected NCEs or biologics with the aim of even earlier postmarketing detection of serious adverse reactions.

Drug Quality Assurance (DQA) Surveillance Program

The DQA program has been the mainstay of CDB's analytical postmarketing surveillance for many years. Recently, novel ways of obtaining drug samples for analyses have been explored and implemented. Instead of the traditional highly labor-intensive samples collected by FDA field investigators, samples have been obtained through a mail-in program from hospital pharmacists. This method of sample collection saves collection time which can be redirected to more critical tasks. Under APPII, CDB will study and pilot test additional mail-in concepts to obtain selected drug product samples, including the mailing of selected drug products by wholesalers directly to a designated FDA laboratory. The study and pilot test will compare mail-in sample results to drug product quality test results from samples formerly collected at the point of manufacture.

Drug Product Problem Reporting (DPPR) Program

The DPPR program seeks to elicit the voluntary reporting of observed or suspected drug product defects by both hospital and community pharmacists. This program has been a valuable adjunct to CDB's analytical postmarketing surveillance activities since 1971. CDB will seek to strengthen the program's analytical postmarketing surveillance aspects to enhance consumer protection against emerging problems and risks with marketed drugs and will, at a minimum, take the following specific actions:

a. Further improve the quality and quantity of DPPR reporting by enlarging the scope and sources of publicity for the program under a proposal for a new DPPR contract;
b. Evaluate the current DPPR ADP systems to improve report handling and follow-up assignments to appropriate FDA components; and
c. Evaluate the role of the DPPR program in relation to the marketing of newly approved chemical entities and the frequency of reported problems occurring with these new approvals.

MEDICAL DEVICES

The Center for Devices and Radiological Health (CDRH) believes strongly that the need for postmarketing surveillance of medical devices is independent of the existence or quality of premarketing review. Premarketing testing occurs under highly controlled conditions with a selected trial population, a limited time span, and limited indications. Many relevant questions (e.g., user experience, rare effects, and device lifetime questions) cannot be addressed until after a device is marketed to the general population. In addition, by law only a small percentage of devices can be given extensive premarketing review while virtually all devices can be given postmarketing review.

Action Plan Phase I included initiatives to strengthen postmarketing surveillance by monitoring implementation of the new medical device reporting (MDR) regulation and by determining (through comparison) if improvements made in the drug adverse reaction system were transferable to the medical device system. The comparison pointed to MDR as being of major importance in the postmarketing surveillance of devices and a system that could benefit from the learning experiences of the drugs ADR systems. The relative maturity of drug postmarketing surveillance systems as well as the relative complexity of postmarketing surveillance for medical devices due to the greater variety of technologies and modes of interaction between devices and device users/patients, did however limit the transferability of improvements.

Under APPII, CDRH will develop a comprehensive philosophy on postmarketing surveillance of medical devices that defines objectives and scope, identifies available and potential data sources, and develops a strategic approach for integrating CDRH's total experience with, and knowledge of, devices. This integration would be reflected in a postmarketing surveillance system that anticipates rather than reacts to device problems and allows CDRH to take a proactive role in protecting the public health.

CDRH's primary objective under APPII will be devising and implementing a strategy for a comprehensive centerwide postmarketing surveillance system for devices that allows CDRH to anticipate and resolve device problems. CDRH has formed a special task group that in the next year will:

a. Define the scope of CDRH's postmarketing surveillance program;
b. Identify sources of postmarketing surveillance information and evaluate how they are currently being used; and
c. Develop options for utilizing/integrating postmarketing information into CDRH's programs.

CDRH will continue implementation of the joint FDA/HCFA (Health Care Financing Administration) Pacemaker Registry. The registry data will be integrated into other appropriate postmarketing surveillance data systems to provide an overall picture of pacemaker and pacemaker lead performance.

FOODS

The Center for Food Safety and Applied Nutrition (CFSAN) will strengthen its Adverse Reaction Monitoring System (ARMS) that stores, retrieves, and analyzes reported adverse health effects associated with food, food and color additives, and vitamin/mineral supplements. This will be accomplished by expanding the system to incorporate information from other relevant data systems such as those from the Centers for Disease Control, the Association of State and Territorial Health Officials, and industry and professional society sponsored adverse food reactions monitoring systems. In addition, CFSAN will encourage more participation both from FDA field personnel and from physicians throughout the United States.

CFSAN will also conduct postmarketing surveillance activities and epidemiological studies that provide information about exposure and possible adverse reactions, including hypersensitivities to food components, contaminants, and nutrients. In particular, CFSAN will review and improve the methods used for the estimation of human intake and exposure to food components by several procedures. One method will consist of developing a contract with the Federation of American Societies for Experimental Biology to convene an expert panel to review data bases and procedures for determining human dietary exposure. Another method, currently in progress, consists of testing the assumptions inherent in a commonly used model to estimate dietary intake of food additives and other food components. A third method will involve collaboration with the National Center for Health Statistics to have input into design of future survey data bases and to assist in analysis of data from national surveys in areas of dietary exposure and diet/health relationships.

CFSAN will continue to contribute toward the National Nutrition Monitoring System by providing information on food labeling practices and public knowledge, attitudes, and preferences concerning foods; and on specific health concerns such as weight loss practices or infant feeding practices.

These activities will help ensure the continued safety of approved food products and additives.

These initiatives under APPII will significantly contribute to *the FDA's ability to enhance consumer protection against new and/or unforeseen risks by effectively monitoring the postmarketing experiences of drugs, devices, and foods.*

4. FOOD SAFETY

FDA will develop and implement an integrated set of initiatives to identify, prevent, and resolve existing and newly emerging public health problems in the Nation's food supply.

One of FDA's major responsibilities is to assure a safe and wholesome food supply. Since unsafe, contaminated or adulterated foods cause illness and death, activities in this area significantly influence the health of Americans. In recent years, rapid technological change and scientific research findings have posed new challenges and opened new opportunities for ensuring the safety of food. The biotechnology revolution, for example, has raised the new challenge of ensuring that the variety of foods or food additives produced through recombinant techniques are safe. But it has also provided the means to create more rapid and precise methods to detect and identify the difficult and continuing problems of microbial contamination of food.

FDA, in its role as gatekeeper of technology transfer from the laboratory to the marketplace, must have an excellent science base and a sustained research program to adequately perform its mission of promoting and protecting the public health by ensuring that the food supply is safe. In addition to maintaining steady progress on food protection issues, FDA must also maintain the capability to rapidly identify health problems and assure that there is flexibility to respond rapidly and effectively to resolve food related health and sanitation crises. Even though the United States has one of the safest food supplies in the world, there is still substantial room for improvement. FDA is committed to further enhancing the safety of the U.S. food supply through APPII.

Significant progress has been made under Action Plan Phase I, including such notable achievements as the establishment of a new adverse reaction monitoring system (ARMS) to track and evaluate consumer complaints, development and publication of a cholesterol labeling proposal, and further strengthening of the new diet/toxicity interactions program. The Agency also responded effectively to a number of unanticipated events, dealing with a wide range of problems, from the potential presence of radionuclides in foods due to the Chernobyl nuclear reactor disaster, to aldicarb in watermelon, and to ethylene glycol in imported wine.

During the 18 month implementation period of APPII, the Center for Food Safety and Applied Nutrition (CFSAN) will not only build upon past efforts but will also undertake major new initiatives. These will include, at a minimum, enhancing the science base which supports regulatory activities across the broad range of food safety concerns, working cooperatively with other Agency components to focus on public education covering food safety and nutrition, ensuring the safety of imported foods, and enhancing the Agency's risk assessment capabilities.

One of the most difficult problems before the Agency is how best to improve the premarketing review process. Though CFSAN has a division responsible for petition review, it has not had a program dedicated primarily to the improvement and smooth functioning of this process In addressing this problem, CFSAN, in a major APPII initiative, has established a new program, Food Additive Petition Review and Policy Development, under the direction of a senior manager. This program will have as its *major* responsibility the development of improved review procedures and policies for food additives, including food packaging, color additives, GRAS substances and products made by new approaches in biotechnology. The primary thrust of this program will be to reduce, where possible, any unnecessary burdens on industry, increase the internal efficiency of the review process, and provide consistency of review while, at the same time, continuing to assure the safety of the nation's food supply.

Under APPII, CFSAN, at a minimum, will undertake a series of initiatives to improve the safety and wholesomeness of the nation's food supply. While these initiatives are broad ranging, CFSAN has divided them into three important categories, Health Problem Identification, Health Problem Prevention, and Health Problem Resolution to stress the new characterization of FDA as principally a public health management organization.

Identified in this manner, the initiatives serve to focus the Agency's responsibility under the Food, Drug, and Cosmetic Act to identify and resolve food related problems; and to stress an important obligation to prevent health problems before they occur. These are all vital areas within which CFSAN must direct its efforts in order to effectively assure a safe and wholesome food supply.

HEALTH PROBLEM IDENTIFICATION

FDA utilizes several mechanisms for identifying potential hazards in the food supply. Most important among these are (1) developing analytical methods and applying them to FDA's surveillance and compliance efforts; (2) engaging in extensive communication and cooperation with professional and consumer groups, industry, and other government agencies; and (3) gathering, analyzing, and monitoring published and unpublished information pertinent to the consumption, quality, and safety of foods. CFSAN will undertake a series of initiatives utilizing these mechanisms to identify additional, heretofore undetected, potential food hazards.

To accomplish these initiatives, CFSAN will conduct state-of-the-art research at the molecular level. The primary purpose of this work is to understand the basic mechanisms, involving both pathogen and host, responsible for various interactions that result in disease, and to develop the most rapid tests possible to detect virulence factors in disease causing microorganisms found in food. These techniques will replace existing, slower and less sensitive microbiological techniques that are not applicable to highly perishable commodities. This work will help to prevent and reduce the incidence of foodborne disease, to reduce the considerable associated costs, and to increase the public's confidence in a safe food supply.

Specific initiatives, at a minimum, will include:

a. The production and field testing of synthetic genetic virulence probes for the important foodborne pathogens: *Listeria monocytogenes, Yersinia enterocolitica,* and detection probes for *Salmonella spp*. This capability will be established in the Agency field laboratories involved in microbiological analyses. CFSAN will also continue to develop genetic probes for seafood toxins. This work will include studies of processes such as depuration, wherein even contaminated shellfish may be "reconditioned" to a safe status.

b. Research on mechanisms of the virulence of pathogens in the food supply. This effort which is directed at developing new methods will be broad ranging and will include "suspected" as well as known "opportunistic" pathogens. One aspect will address the feasibility of using animal models to mimic predisposing conditions in humans. In another approach, non-acute disease causing bacteria will be studied to investigate the mechanisms involved in opportunistic infections that are frequently encountered in high numbers in foods. Studies will also be conducted to determine how pathogens found in the food supply thwart the immune system in some people, thereby triggering a variety of chronic diseases. This work is an outgrowth of the recent Chicago milk-borne salmonellosis outbreak in which about 180,000 people were directly affected, including 2 deaths and over 4,000 hospitalizations. Slightly over 2% of the 16,000 confirmed salmonellosis illnesses had symptoms compatible with reactive arthritis. To begin the study of this aspect of pathogenicity, a systematic search for peptide sequences responsible for arthritis induction by certain Gram-negative foodborne pathogens will be conducted using appropriate *in vitro* systems, as well as studies on chronic sequelae to acute gastroenteritis (e.g., Guillaine-Barre syndrome). This effort expands current approaches of addressing acute and chronic aspects of pathogenicity to the much longer term multigenerational effects of pathogenicity.

c. Another research initiative will involve complete purification and production of the dinoflagellate toxin(s) PSP which accumulates in shellfish. This work is intended to result in better detection of PSP. CFSAN will also establish a culture system for ciguatera toxin, another dinoflagellate toxin that accumulates in fish. These and other dinoflagellate and algal toxins will be studied for other toxicological effects since many of these are potent tumor promoters (e.g., aplysiatoxin).

d. To provide a more rational basis on the threshold of regulation for biotechnology products, CFSAN will conduct research on the composition of food to investigate the extrinsic and intrinsic components of food. It will investigate factors which affect the nutrient character of food, as well as carcinogens, mutagens, and teratogens and other naturally occurring substances that may be harmful or even protective. The results of these efforts will increase CFSAN's knowledge of the food matrix and of the interactions and transformations of food components, and allow for a better understanding of the nutritional and toxicological quality of biotechnologically produced and fabricated foods.

e. Research will also be conducted on the development of new methods for assessing the quality of nutrients and other valued components of food. This research will enhance both government and industry efforts to provide information about foods through labeling. The studies outlined below, will have a direct bearing on the Agency's review of food labeling and fortification policy regulations. In particular, work will be undertaken, at a minimum, to:
   - Study the effects of processing on the physical and chemical properties of food components such as lipids and dietary fiber;
   - Identify and analyze foods for non-nutrient components, and study the impact of these substances on food quality both before and after processing;
   - Investigate for regulatory purposes, methods to detect whether food has been irradiated;
   - Develop methods, in collaboration with outside laboratories, for measuring the biologically active forms of nutrients, vitamins and components of dietary fiber; and
   - Develop policy papers on the safety and regulation of novel foods, including foods for special medical uses.

f. CFSAN will continue to maintain communication with organizations outside FDA in order to identify, through cooperative means, potential health hazards. This communication is a vital link in helping to identify and deal with the myriad of potential food problems. Two significant examples of cooperative efforts are sulfites and food tampering. The adverse effects produced by sulfites led to the establishment of an advisory committee on hypersensitivity to food ingredients. The committee made several recommendations to the Agency. Another major problem that required cooperative efforts involved the complex issue of food tampering. The Agency met on several occasions with consumer groups, health professional representatives, trade associations, industry representatives, state and local health authorities, and packagers to identify and take steps to resolve problems of food tampering. Under APPII, CFSAN will continue to pursue and identify potential health problems by maintaining open and cooperative forms of communication with these organizations.

g. CFSAN also keeps abreast of published and unpublished information on foods to maintain current expertise on the safety of foods and food ingredients. Specifically, CFSAN contracts with the Federation of American Societies for Experimental Biology (FASEB), which utilizes expert panels to identify potential problems through literature review. This effort will be expanded in APPII to include, at a minimum, the development of a series of GRAS review documents. Also in APPII, in addition to maintaining the inventory of current compounds, CFSAN will expand this inventory to new foods and food ingredients. Through reviewing information obtained from the strengthened National Nutrition Monitoring System, CFSAN will continue to monitor adverse reaction reports for potential health hazards associated with food, food and color additives, and vitamin/mineral supplements as identified in Goal 3—Postmarketing Surveillance.

HEALTH PROBLEM PREVENTION

In addition to establishing policies and procedures related to premarket approval of food substances to ensure a safe food supply, CFSAN has a strong obligation to promote and protect the public health through other preventive means. This includes assessment of "potential" risks and the development of policies to avoid such risks as well as assuring that the American public is fully informed on all major food issues that have a potential impact on their health. To effectively deal with health problems through preventive means, CFSAN will, at a minimum, take the following actions:

a. Initiate a new program for food and color additive petition review and policy development. The establishment of this program is a significant move toward improving the food and color additive petition review process while continuing to assure the safe use of food and color additives. CFSAN, through this program, is commited to addressing three critical areas in the review process. They are the need to reduce or eliminate any burden on industry resulting from review process requirements that may be unwarranted, assure that there is consistency in all reviews and policies, and improve the internal efficiency of all reviews. CFSAN will work to reduce or eliminate any burden on industry and assure consistency. The center will develop a consistent basis upon which to determine those situations where industry may not even need to submit a formal petition. In those situations where a formal petition is required, the center will clarify and standardize data requirements eliminating those that are no longer necessary by scaling information necessary to establish safety to the particular situation under review. Actions taken to accomplish these improvements include the following:

- Develop a "Threshold of Regulation" policy paper for food contact situations involving potentially *de minimis* levels of migration (i.e., levels below those necessary to satisfy the food additive definition of the FD&C Act). CFSAN will also explore the feasibility of holding a joint workshop with the Food and Drug Law Institute and the Toxicology Forum to jointly consider with industry how best to implement a *de minimis* approach to regulation;
- Update the criteria and standards for the safety assessment of food and color additives as contained in *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food*, generally referred to as the "Redbook"; and
- Conduct research studies to provide a scientific basis for the establishment of guidelines for the development and use of physiologically based pharmacokinetic data in the safety evaluation of food and color additives.

Although CFSAN generally has been able, with a small amount of resources, to process petitions within statutory deadlines, budgetary pressures on government and the private sector make it more critical to increase the efficiency of the review process. CFSAN will explore innovative ways to make the petition review process faster and less labor intensive. This will include ways of automating aspects of the review, including accepting data from petitioners in machine-readable form and clarifying the requirements of the process. Furthermore, the center will develop a comprehensive computer database on the migration of chemical substances from food packaging materials. Such a database will save considerable time in the petition review process and ensure that FDA's regulatory decisions are based on the most current science:

b. Reinstate a preventive approach to pathogens in food by reestablishing the General Pathogen Surveillance Program. This program will utilize state-of-the-art analysis tools such as genetic probes and monoclonal antibody techniques. These new techniques will allow for more rapid identification, isolation, and resolution of future potential microbial food contamination problems. These techniques will be particularly useful for determining microbial organisms that are traditionally known to invade fish and shellfish.
c. Recognize the growth in the use of new packaging materials and conduct research to investigate the safety of extended shelf-life foods, such as those packaged in altered atmospheres and those relying largely on refrigeration. Safety studies will include the growth and toxin production, where appropriate, of *Shigella* and *Clostridium botulinum*, as well as "psychrophilic pathogens" such as *Aeronomas, Listeria* and *Yersina*. Such studies are aimed at developing information on extended shelf-life products to allow the Agency, if necessary, to institute preventive measures to assure that they are free from microbial contamination.
d. Emphasize a new initiative to study diet/toxicity interactions. This initiative includes a study, in collaboration with other organizations within FDA and PHS, of the beneficial and adverse effects of combinations of dietary components and nutrients. The knowledge gained will enable the Agency to play an important role in disease prevention by informing the public about good diet and nutrition.
e. Continue to actively promote the dissemination of health protection information. CFSAN will strengthen through the establishment of a new Technical Assistance Program its efforts to provide technical assistance to the states, local governments, industry, foreign governments, international organizations, other federal agencies, and the public on matters concerning food safety. FDA's unique expertise, experience, and information will be used in a highly leveraged way through cooperative arrangements, training, and other forms of oral and written communication. The dissemination of this information will aid other organizations and nations in effectively carrying out their responsibilities in ensuring food safety.
f. Plan an overall strategy for and implement an information campaign on foodborne disease, its consequences and the safe handling of food.
g. Actively pursue major initiatives such as the comprehensive awareness programs dealing with sodium and cholesterol labelling. These programs are intended to inform and educate the consumer on major issues of importance to good health.

HEALTH PROBLEM RESOLUTION

The Agency has recognized that microbial contamination of food poses a significant problem at this time. Accordingly FDA will focus major efforts on resolving microbial contamination problems while still continuing to respond to concerns with pesticides and chemicals. Efforts will be directed through the combined Agency approach on Risk Assessment (see Goal 8) to provide a current index of relative risks associated with the consumption of food. CFSAN will continue to improve its efforts to assure that immediate and effective steps are taken to resolve health problems that arise with the food supply. Specifically, CFSAN will, at a minimum, take the following actions to resolve pathogenic contamination problems currently being experienced by the dairy industry:

a. Determine the adequacy of the Pasteurized Milk Ordinance regarding the pasteurization time/temperature relationship for *Listeria monocytogenes* and *Yersina enterocolitica* using commercial scale pasteurization equipment;
b. Determine the adequacy of the current phosphatase method to detect raw milk adulteration or under-pasteurization in soft-ripened and blue veined cheeses. The method will be modified to overcome observed problems from microbial phosphatases which give false positive results; and
c. Complete the surveillance of the total U.S. dairy industry to fully remedy the current contamination problems.

CFSAN will continue its efforts to improve the Agency's capability to respond to and resolve contamination of the food supply by pesticides or chemical contaminants. Traditionally, compliance investigations have been limited by the slowness of current analytical methods. Under these circumstances, food that is produced and rapidly released into distribution makes enforcement particularly difficult. For this reason, CFSAN is emphasizing the development of shorter and more efficient procedures for detection of these contaminants. These new procedures will allow for improved responsiveness and greater flexibility in applying Agency enforcement strategies that may range from seizure to voluntary compliance. Particular emphasis will be placed on the expansion of multi-residue methods for pesticides, and on the further development of methods to determine a broad range of metals and other elements in a single analysis. In addition, improvements will be made to speed up the summarization, evaluation, and dissemination of findings. CFSAN will focus on applying these measures to imported foods through revised import and enforcement programs (see also, Goal 6—Enforcement and Goal 7—Imports).

CFSAN will, through the accomplishment of these major initiatives addressing the *identification*, the *prevention*, and the *resolution* of health problems, have *a significant impact on assuring a safe and wholesome food supply for the American public.*

5. VETERINARY PRODUCT SAFETY

FDA will develop and implement an integrated program of initiatives and activities to identify, prevent, and resolve existing and emerging health problems related to the manufacturing, distribution, and use of animal drugs and feed additives.

A major responsibility of FDA is to assure that animal drugs and feed additives are safe and effective for their intended purposes and that meat and eggs derived from treated animals will be free from potentially harmful or otherwise illegal residues. These responsibilities are fulfilled by FDA's Center for Veterinary Medicine (CVM) through premarketing product review and through postmarketing surveillance and compliance activities. CVM's APPII initiatives will be carried out in the context of Health Problem Identification, Health Problem Prevention, and Health Problem Resolution.

HEALTH PROBLEM IDENTIFICATION

Focusing primarily on information gathering and analysis, CVM will utilize a number of mechanisms and processes to identify, characterize, and quantify veterinary drug and feed additive problems to be addressed under APPII.

Knowledge about marketed animal drugs including type, approval status, amount, and expected use patterns, sources, and methods of distribution is critical to the development of problem prevention and resolution strategies designed to curtail illegal sale, distribution, and use of animal drugs and feed additives.

CVM will significantly enhance its postmarketing surveillance activities to provide greater protection against new and heretofore unforeseen risks involving marketed products.

Specifically CVM will, at a minimum, establish extensive communications and liaison interfaces with appropriate constituencies including: the United States Department of Agriculture (USDA); the Environmental Protection Agency (EPA); professional organizations, such as the American Veterinary Medical Association (AVMA) and allied veterinary medical specialty groups; trade associations and consumer groups; livestock producers; and others. Working collaboratively with USDA, CVM will develop methods to identify and track the processing of animals through each stage of the production and distribution cycle. Information will also be gathered through FDA investigations and from state and local authorities. As a major part of this activity, CVM will utilize an on-line automated data processing system to store, process, and analyze drug listing information. These, coupled with automated systems for processing and analyzing adverse drug reaction and drug experience reports, will enable CVM to analyze for relative risk and develop and focus problem prevention and resolution strategies.

The tissue residue program will be supported by an extensive, broad-base program of intramural and extramural research designed to develop and validate new and/or improved analytical methods for the detection and quantification of residues of animal drugs in the tissues of treated animals or poultry.

Both FDA and USDA share the responsibility for animal drug residue monitoring of animal-derived human food and the subsequent follow-up actions to bring about correction. The problems and public concerns associated with drug residues were highlighted in a recent National Academy of Science report which recommended more focused efforts toward prevention of residues and better communications between the responsible agencies. Accordingly, CVM has taken the lead in establishing an interagency tissue residue regulatory task force to identify and characterize tissue residue problems and to function as a steering group for focused review of prevention and resolution strategies. The task force, which includes representatives from FDA and USDA, will analyze information from FDA inspections, USDA monitoring programs, state and local authorities and other sources, to define and characterize sources of residues, products most commonly affected, and producer and processor strategies for handling and marketing high risk animals (animals likely to contain violative residues).

In addition, CVM has established a separate interagency residue analytical methods task force, consisting of representatives from FDA and USDA, as well as representatives from the Association of Official Analytical Chemists (AOAC) and from state analytical laboratories, to identify and characterize needs for new and/or improved analytical methods for identification, characterization, and quantification of animal drug residues in edible animal tissues.

HEALTH PROBLEM PREVENTION

At the heart of CVM's efforts to prevent human health problems associated with the use of animal drugs and feed additives is its established animal drug review process. In order to increase the availability of approved, safe and effective animal drugs, CVM will, under APPII, undertake major new initiatives to streamline the new animal drug application (NADA) submission and review process. These new initiatives will result in an enhancement of the quality of industry submissions resulting in improvements in the timeliness, effectiveness, and efficiency of CVM's reviews, and will allow for the use of foreign data in support of NADAs, thus reducing the burden of duplicating research already done. These efforts will include a reduction in the number of supplemental changes to currently marketed drugs requiring preapproval by the Agency. They will also include a phased review process under which data review by CVM will begin during the investigational stages of new drug development. These changes will result in a more efficient and higher quality drug review process, enabling CVM to approve on a timely basis safer and more efficacious drugs for animal use, benefiting the American public.

As part of the tissue residue program, CVM will develop and implement a plan for tissue residue prevention initiatives. These efforts will include significant new industry relation and education initiatives, making maximum use of joint FDA/industry informational and educational seminars and symposia. It will also feature jointly-developed informational and educational materials which will be distributed through *CVM Update* mailings and articles in the *FDA Veterinarian*, as well as through industry/producer newsletters, journals, and mailings. CVM will also work directly with livestock producer organizations, food animal veterinary medical specialty groups, and the USDA to develop and implement farm-site quality assurance programs particularly strengthening efforts at individual animal identification and associated producer accountability and the use of new drug detection/screening kits.

Complementing these programs will be the development and implementation of an extensive broad-based program of intramural and extramural research focused on developing new and/or improved analytical methods for the detection, characterization, and quantification of residues of significant animal drugs in meat, milk, and eggs. The program will include (1) intensive efforts aimed at determining the drugs for which new or improved analytical methods are needed, (2) research planning activities, and (3) methods validation trials aimed at proving the utility of each method.

HEALTH PROBLEM RESOLUTION

New health problem resolution initiatives to be undertaken by CVM under APPII will, at a minimum, focus primarily on two efforts:

1. Reducing the incidence of illegal drug residues; and
2. Resolving the problem of illegal sales, distribution, and use of animal drugs.

In the drug residue program, CVM will, in conjunction with FDA field offices and USDA, develop and implement a compliance/enforcement program for focusing resources and effort on repeat offender producers, on problem commodity classes such as veal calves and cull dairy cows, on problem meat plants which have been identified as processors of "high risk" livestock, and on problem regions or areas identified through health problem identification initiatives. The program will be designed to most effectively and efficiently develop case material to support legal enforcement actions.

Also under APPII, CVM will undertake major new initiatives to control the illegal sale, distribution, and use of animal drugs and feed additives. These initiatives will include the development of model state codes, innovative enforcement strategies to control the illegal importation of bulk animal drugs, and the negotiation of federal/state regulatory contracts.

CVM will, in conjunction with FDA field offices and state regulatory officials, develop and implement a second compliance/enforcement program for focusing resources and effort on illegal drug manufacturer/distributors, illegal drug importers (including animal drug smugglers), and others trading in illegal animal drug markets. The program will be designed to most effectively and efficiently develop case material to support legal enforcement actions. In addition, CVM will mount a major initiative to encourage state boards of veterinary medicine, state boards of pharmacy, and state departments of agriculture and health to become actively involved in the oversight of animal drug distribution and use systems, thereby, greatly facilitating the resolution of the public health problem. A major educational effort concerning drug residues in livestock will be expanded to provide further resolution of persistent residue problems. This initiative is discussed further in Goal 10—Information, Education, and Technical Assistance.

Also CVM will expand and enhance a highly successful pilot state contract initiative to curb the illegal sale, distribution, and use of animal drugs at the state level. The program is aimed at surveying drug sales, distribution, and use patterns at the state level and focuses on timely and effective regulatory follow-up by state regulatory authorities. Under this program the effectiveness of regulatory initiatives as an incentive to voluntary compliance and thus prevention of illegal trade will be greatly enhanced. The proper distribution and use of important animal drugs and feed additives will result in reductions in the potential for occurrence of harmful residues in food, thus, improving protection of the public health.

Thus under APPII, CVM will enter into *major new initiatives in the regulation of animal drugs and feed additives designed to both serve animal health needs and to assure the production of abundant and wholesome animal-derived food products for sustaining the health of the American public.*

6. ENFORCEMENT

FDA will develop specific initiatives to improve its enforcement processes, to streamline enforcement procedures and to clarify its enforcement policies so as to provide more reasoned and uniform enforcement actions throughout the Agency.

FDA's primary mission is to protect the health and welfare of the American public by assuring the safety, wholesomeness, effectiveness, and truthful labeling of the drugs, foods, and medical devices used in this country. The Agency accomplishes this mission using educational, voluntary compliance, and regulatory approaches, including enforcement. When a major public health problem occurs that can be prevented or corrected entirely by users of a product, an information, education, or technical assistance approach is generally most appropriate. On the other hand, regulatory action is most generally appropriate when the major public health problem is associated with the design, manufacturing, distribution, or labeling of the product. In these situations the problem can best be prevented or corrected by involved manufacturers or distributors. When a regulatory approach is used, numerous alternatives are available including, where appropriate, less onerous administrative actions such as issuing a notice of adverse findings (NAF) letter, publicizing violative acts, obtaining agreements from businesses to suspend operations, and issuing orders to businesses to apply for emergency permits to ship products. Regulatory alternatives may also include, where appropriate, legal sanctions such as criminal prosecutions, civil penalties, seizure of products to remove them from distribution channels, and injunctions to restrain businesses from shipping violative products.

Enforcement actions are taken to protect the public health and well being by removing unsafe or otherwise illegal products from the marketplace and by deterring future violations. The particular method of enforcement chosen on a case-by-case basis is intended to accomplish one or both of these goals. The prompt processing of enforcement actions is clearly in the interest of consumers, legitimate businesses regulated by FDA, and the courts. Prompt enforcement actions assure businesses of a fair competitive environment because they may rely on recognized regulatory standards.

FDA has an enviable reputation as an effective consumer protection agency; however, changing conditions make it difficult to maintain expertise in processing of enforcement actions. These conditions include the introduction of new product and manufacturing technologies, new types of violations which involve deliberate criminal conduct, expanded expectations of Congress and the public for effective risk management, the increasing need to minimize unintended economic consequences, the need for a more sophisticated inspectional force, and the need to manage scarce resources most efficiently. Agency managers are acutely aware of the importance and impact of these changing conditions as the Agency has dealt with tampering investigations, the marketing of drugs of unknown origin and quality including counterfeits, the illegal sale of veterinary prescription drugs, and the microbiological contamination of dairy products.

As part of Action Plan Phase II, FDA, at a minimum, will undertake initiatives to assure the effective, efficient, and timely execution of reasoned and uniform enforcement actions when they are necessary. These initiatives are needed to cope with increasing demands and decreasing resources. They will focus both on the substance and on the processes of regulatory actions and will include:

Guidance Materials

The Office of Regulatory Affairs (ORA) will initiate appropriate changes in guidance materials and revise FDA policy and procedures to facilitate more timely processing and prompt decisionmaking. For example, FDA's internal policy guidance will be clarified to help compliance officials better understand the degree of prior notice a business should receive before enforcement action is initiated. There will be a greater reliance on NAF letters (in lieu of regulatory letters) to provide warnings about objectionable conditions and to expedite voluntary correction. Both types of letters have equal weight in providing notice of violations; however, regulatory letters require a higher level of review (i.e., headquarters) because they include a promise to initiate action if correction is not made. Consequently, NAF letters can generally be issued more promptly thus accelerating the desired public health measures. In addition, processes governing the submission of recommendations for legal actions will be modified to eliminate duplicate review of facts, and thereby expedite the process.

Decision Process

A process of concurrent (parallel) instead of sequential (serial) review of enforcement action recommendations will be implemented where appropriate to substantially reduce processing time for important legal actions. Currently, field or headquarters managers may request that a committee comprised of senior compliance officials immediately review an action recommendation when they believe the action must be expedited due to the urgency or complexity of the matter. Steps will be taken to better utilize such ad hoc committees to resolve substantive and complex issues and thereby permit decision-makers to quickly arrive at consensus Agency decisions regarding enforcement actions.

Utilization of Personnel

FDA will initiate a greater interchange/exchange between field and headquarters employees. Special enforcement teams will be utilized to address unique enforcement problems, especially those that involve highly technical industry problems. Enforcement teams and national coordinators will be designated when necessary to conduct criminal investigations of nationwide schemes that violate the law. Special training will be provided for field and center compliance personnel to develop expertise particularly in investigations involving fraud and intentional violations and to expedite enforcement actions. Where appropriate, FDA will actively seek the support of scientific and enforcement components of HHS, the Department of Justice, and other Federal agencies.

Processing Efficiencies

The need for an automated policy/precedent information system will be assessed, as well as the need for updated word processing and communication equipment to process enforcement actions more timely, efficiently, and effectively. The Office of Management and Operations and ORA will determine the cost and benefits of these systems and equipment and make recommendations for action, recognizing that they may require significant Agency monetary and personnel resources.

Automated information systems for monitoring enforcement actions throughout the Agency will be implemented to further enhance FDA enforcement coordination. Special reports will be submitted regularly by the field to ORA, identifying specific delays in processing of enforcement action recommendations. Agency components will develop mechanisms to enhance communication, resolve workload problems which may contribute to delays, and articulate priorities. Steps will be taken to better coordinate activities to expedite enforcement actions.

Coordination

FDA will continue to improve its already strong working relationships with state regulatory agencies and with the Department of Justice. Particular focus will be directed to networking with state health officials. Sharing information with state officials facilitates cooperative investigations and the targeting of violations for either state or federal enforcement actions. Coordinating major investigations with Department of Justice officials assures the selection of mutually acceptable courses of action and the prompt handling of recommendations.

Quality Assurance

Working with other Agency components, ORA will initiate an enforcement quality assurance program to ensure continued high-quality investigations and enforcement activities. Reviews based on commonly accepted quality standards will facilitate processing enforcement actions. Quality of individual actions will be assessed on a case-by-case basis by the centers. ORA will coordinate center activities, determine trends, and be the focal point for communications to maintain a high quality of enforcement actions throughout the Agency, *thereby providing more reasoned and uniform enforcement actions throughout the Agency.*

7. IMPORTS

FDA will improve the coverage of imported products through improved intra-and inter-agency communications, increased use of automated programs, greater efforts to obtain more reasoned and uniform import enforcement actions throughout the Agency, and improved laboratories in the field to facilitate sample analyses.

The number of consumer products that are imported from outside the United States has increased three-fold since the mid 1970's—from 500,000 to 1.4 million distinct entries—and continues to increase. This trend includes foods, drugs, medical devices, and other FDA regulated commodities. The most recent U.S. Customs Department data indicate that entries of FDA regulated products for 1984 were in excess of 1.4 million. The Agency has historically estimated at least a 5% annual increase in import entries. Therefore 1987 shipments are projected to be somewhat in excess of 1.6 million entries.

More imported FDA regulated products are now in ready-to-use consumer packages and undergo no further processing by manufacturers inside U.S. borders. *Since the Agency has limited authority to inspect foreign manufacturers, the extent of its understanding of the circumstances under which these foods and drugs were prepared, packaged, or stored before entry is in direct contrast to that of products produced by domestic manufacturers.* For example, the largest resource expenditure for domestic food sanitation is the on-site inspection of manufacturing facilities. Product sampling and analysis is used as an adjunct in many cases in support of the on-site quality assessment made by FDA investigators.

Recognizing that coverage on entry is the primary practical means of determining product quality, the reduction of import coverage from a 20% level for all entries in the mid 1970s to the current projected level of about 9% causes FDA serious concern. The reduction is due primarily to the growth in entries from an earlier level of about 500,000 to the approximately 1.6 million projected above. Of the total entries, approximately 84% were foods, 10% medical devices, 3% human drugs, and 3% veterinary drugs.

As a result, the level of confidence in the purity and safety of domestic products is of a much higher order than the level of confidence in imported products. With the increasing importance of imported products in the consumer's diet and health care, this disparity in confidence levels must be addressed.

FDA will address these concerns by undertaking the following initiatives under the lead of the Office of Regulatory Affairs (ORA):

Import Targeting

Additional Agency efforts to target coverage on proven poor quality products and their importers will be undertaken promptly. To accomplish this, ORA and the Center for Food Safety and Applied Nutrition (CFSAN), have agreed on both short-term and long-term steps, which will begin in early 1987. The short-term steps, at a minimum, include:

a. Reprogramming resources from domestic programs to import programs;
b. Using existing product data to target specific products for sampling and, where appropriate, automatic detention;
c. Concentrating coverage of ports, products, countries, or brokers by district personnel at specified times to demonstrate Agency "presence" and focusing on selected program areas;
d. Increasing the number of imported products covered during domestic work; and
e. Enhancing field laboratory capabilities to process samples of imported products.

Long-term steps, at a minimum, include further development of memoranda of understanding (MOUs) with foreign governments, increased inspection of foreign manufacturers where possible, expanded efforts to obtain state assistance through contract or agreement, and broader use of automatic detentions of violative products. ORA, the centers, and the Office of Health Affairs will coordinate these long-term steps.

Total Import Information/Detention System

ORA will design and install a single comprehensive import data system that will provide up to the minute information regarding violative products, track shipments under review, automatically generate notices to brokers/importers, and identify trends and significant problem products.

In the modern import environment it is critical that information on violative products be relayed rapidly between districts, headquarters, and the U.S. Customs Service. The current import detention system, while serving its purpose, is incomplete and has been outstripped by the events of recent years. The system design is obsolete, too slow, and current hard copy reporting does not lend itself to rapid, comprehensive, easy, or uniform communication or interpretation.

The necessary elements of a complete import information system have been studied by ORA with the assistance of a private contractor. Under Action Plan Phase II (APPII), ORA will establish a project team to review the contract study recommendations and other ORA studies to select those recommendations that will be the foundation of the new import information system.

District Import Paperwork Flow

ORA will conduct a study of the current import paperwork systems used in the districts. The mushrooming number of entries in the last decade has meant an ever increasing quantity of processed paper to be reviewed and stored since each entry results in one or more forms for review. Further, the existing paperwork system was designed over 10 years ago, before automated work stations were widely available. Methods will be devised for streamlining and improving operations for resource savings. For example, shortening and consolidating certain forms and elimination of others should result in simplified processing and increased efficiencies.

Import Enforcement Procedures

ORA will reexamine import enforcement procedures and update them where appropriate to promote more reasoned and uniform enforcement and improved communication between districts. Interim guidance currently exists for revised procedures in the areas of timeframes, automatic detention, examination of refused goods, private laboratories representing importers, import information directives, cargo control procedures, and enforcement approaches for problem importers. Under APPII the interim guidance will be refined as necessary, finalized, and implemented.

Import Alert System

ORA will improve the timeliness of distribution of import alert information to the field and make alerts more user friendly.

Although electronic distribution of import alerts is now in use, they are not always immediately available for the entry reviewer or resident post personnel. Also, the contents of import alerts cannot be searched easily for specifics such as manufacturer, product, or nature of public health problem, either by name or by other helpful parameter.

ORA has been studying and testing the FDA Import Alert Retrieval System (FIARS) which would allow computerized access and search capabilities by reviewers of the hundreds of import alerts currently in effect. In addition, this system can be used to store other documents such as import bulletins and local district directives. As a commitment under APPII, ORA will make full implementation of this data system a field-wide reality during FY 87.

These initiatives under APPII will significantly enhance the *FDA's ability to cope with the vastly increased number of imports and with major technological changes in manufacturing in the United States and abroad.*

8. RISK ASSESSMENT

FDA will expand the risk assessment initiatives, begun during Action Plan Phase I, to improve the peer review/scientific base upon which risk assessments and consequently risk management decisions are made and will develop and implement processes to insure that its uses of risk assessment techniques in carrying out its regulatory responsibilities contribute to promoting public health in a timely, effective, and efficient manner.

FDA's ability to protect the health of consumers as they are exposed to the products under its jurisdiction can be no better than its ability to assess the risks associated with those exposures. Too often consumers are confused by conflicting statements of human risk and do not understand the extraordinarily large range of uncertainty which generally surrounds estimates of risk.

ACHIEVEMENTS UNDER ACTION PLAN PHASE I

FDA undertook initiatives under Action Plan Phase I both to enhance its ability to assess the risks associated with consumer exposure to FDA regulated products and to improve its capability for informing consumers about the scientifically necessary uncertainties involved in risk assessment decisions. Several notable successes were achieved in improving the scientific basis upon which risk assessments were made and in applying these risk assessments to judgements on specific consumer products.

FDA applied a carefully reasoned process of risk assessment in a proposed regulation published on December 18, 1985, which would ban the use of the chemical *methylene chloride* in cosmetic products. On the one hand, methylene chloride is used in a variety of consumer and industrial products as a solvent and flame suppressant, especially in hair sprays. Based on studies indicating the inhalation of methylene chloride causes cancer in laboratory animals, FDA concluded *that the risk of cancer from continued use of this chemical in cosmetics was sufficiently high as to pose a significant risk to the public health*. On the other hand, methylene chloride is also used as an extraction solvent to remove caffeine from coffee. FDA found *the extremely low residual level of methylene chloride in decaffeinated coffee to present virtually no human health risk, and therefore concluded that no additional restrictions on this use would be needed to protect the public health*.

The Agency's handling of methylene chloride represents one application of the *de minimis* principle (i.e., a principle of law stipulating that the law does not concern itself with trifles). In another application of this principle, final rules were recently published permanently listing the color additives D&C Orange No. 17 and D&C Red No. 19 for external application. FDA has been "provisionally listing" a number of *color additives* to allow for the completion and evaluation of studies of the safety of the use of these additives. To aid its decisionmaking on the provisionally listed color additives, FDA established a panel of experts to review the safety data on FD&C Red No. 3, D&C Red Nos. 8, 9, 19, and 37 and D&C Orange No. 17. This panel was asked to determine whether it is possible to quantify the carcinogenic risk presented by the use of these color additives, and if so, what the levels of risk are. The Agency received and reviewed a final peer-reviewed report on these color additives. FDA's final action on Orange No. 17 and Red No. 19 was based on the conclusion *that the risk posed by use of these substances is so trivial as to represent virtually no real threat of cancer to the public*.

FDA's Action Plan Phase I provided for the development of a comprehensive research program across FDA to evaluate and test, where practical, the assumptions used in risk assessment and to coordinate this effort with other federal agencies. To achieve this, a risk assessment policy committee was formed under the leadership of the Director of the National Center for Toxicological Research (NCTR), to develop a comprehensive plan for evaluation and testing of the assumptions underlying risk assessment. The membership of this committee includes scientists from each of FDA's centers. As one part of the comprehensive plan, NCTR has completed a major portion of an experimental risk assessment plan and has established protocols to refine biomarkers of toxic insult, nutritional modulators of toxicity, and biostatistical study of risk assessment.

Because all of FDA's centers are involved in assessing and managing risks (as part of their public health problem identification and resolution efforts), the Agency is seeking to improve current risk assessment procedures and techniques. Accordingly, NCTR is coordinating *collaborative research*:

(1) to improve understanding of the chemical reactions occurring in the human body in association with a toxic chemical; (2) to develop markers in the human body that can be used to demonstrate prior exposure to toxic chemicals; (3) to improve the design of scientific testing particularly in areas involving extrapolating from the results of animal studies to the likely effects upon humans; and (4) to conserve resources and share technological information with other government or private research laboratories.

IMPORTANT RISK ASSESSMENT ELEMENTS

FDA will continue its high priority attention to improving risk assessment techniques, making more reasoned and uniform regulatory decisions, and promoting the public health in an effective and efficient manner. Actions begun under Action Plan Phase I will continue and significant new initiatives will be undertaken under APPII. The following eight elements are helpful in understanding the great need for new initiatives:

1. *Clearing Uncertainty*. In the area of toxic chemicals, scientific knowledge has not progressed to where the risks to human health can be definitively stated. In the absence of better scientific information, toxic chemical risk assessors, world wide, have bridged information gaps with a host of unproven generic assumptions, of which some 50-odd have been utilized to date. It has been estimated that the resulting risk assessments, upon which decision makers currently rely, may be in error by several orders of magnitude, overestimating, in most situations, the size of risks present. This process is inadequate for properly informing and protecting consumers, it is costly, and it will become less adequate in the future if not improved. Clearly, improvements in the process must be developed and utilized in the near term;
2. *Elucidating Biological Mechanisms*. To adopt a problem-solving approach (rather than continuing to rely only on the problem-identification approach of simply finding more and more chemicals that are toxic in animals at mega doses), it is necessary to understand the biological causes of adverse effects of chemicals on human health. In the case of toxic chemicals, a major problem is that the biological mechanisms responsible for cancer, birth defects, and other human disease states have not yet been totally elucidated. The breadth of scientific knowledge required to do this cannot be obtained exclusively from testing animals to observe endpoints such as cancer development. Therefore, FDA's approach is directed toward understanding the specific steps in the biological mechanisms that result in disease and, in the case of medical devices, adding an understanding of concerns associated with engineering, physics and electronics;
3. *Scientific Advancements*. Scientific tools are becoming more readily available that can dramatically improve present risk estimates. Progress in the scientific discipline of molecular biology has made possible an understanding of sub-cellular biochemistry and cellular reproduction at a level far more detailed than has been possible previously. Through this better understanding, FDA scientists are provided knowledge of both human and laboratory animal processes which consequently provide the ability to compare results of exposure from laboratory animals to humans. There is great promise with the maturing of the newer scientific techniques. With that promise comes the responsibility to devote the effort necessary to optimize the new technology, to lessen the degree of uncertainty, and more adequately understand and assess risks. The research directed to this effort represents an investment whose dividends will be improved future risk assessments;
4. *Utilization of National Capability*. These scientific activities, with such a major public health impact, are amenable to a concerted, cooperative research effort utilizing the combined scientific talents of academia, industry, and public interest groups. FDA will adopt innovative arrangements with academia to utilize the significant talents of that sector, but also to encourage collaborative efforts where university laboratories work with FDA to help solve specific scientific problems. This process must be open to all groups who have solid data to contribute and must be overseen by an unbiased peer review system of the highest scientific quality and integrity;
5. *Realistic Communications*. FDA has the difficult task of communicating the complexities of risk assessment to the public and to regulated industry. The confusion resulting from the finding that many chemicals are toxic in rodents at large doses and conflicting statements of human risk, has taken its toll on consumer confidence and government credibility. Many consumers do not understand the relatively large range of uncertainty surrounding extant best estimates of risk. To communicate the limitations in our scientific knowledge, the significance of the uncertainties in assessing risk, as well as the advances as they occur, requires more attention;
6. *Peer Review*. To assure the public and industry that every effort is being made to incorporate new scientific methods and statistical procedures into FDA's risk assessment processes, regular peer-review of internal efforts must also be evident. Since the basis of this program is scientific, there is a primary need for confidence in the science used. The most effective method of assuring scientific confidence in a process is through external, unbiased peer review of the highest quality;
7. *HHS Task Force*. Due to HHS concern for risk assessment issues, a Task Force on Risk Assessment and Risk Management of Toxic Substances was convened by the Secretary in 1985. This task force:

a. Investigated and reported the state of scientific knowledge and limitations in this area;

b. Described the activities of HHS in risk assessment and risk management; and

c. Provided a plan of action for solving the set of risk assessment problems identified.

FDA has continued the work of that task force as reflected by the prominence of risk assessment in both Action Plan Phase I and APPII. An important set of activities is the implementation of the guidelines developed by the task force. These guidelines for conducting risk assessments are well considered and each FDA center will develop an implementation plan for implementing them which will be merged into an Agency set of policies. The public and regulated industry deserve a full understanding of the processes FDA utilizes in assessing risks. This effort will also serve to help attain uniformity of processes and procedures in the risk assessment process used by FDA as well as the EPA, CPSC, OSHA, and others; and

8. *Medical Devices*. Although historically risk assessment has been associated with toxic substances, it clearly includes other concerns as well. The medical devices program is one such important area where toxicological risk must be assessed, but the risk of device failure (i.e., mechanical or electrical), the impact on the delivery of health care of any failure, and the role of the user who handles the devices must also be assessed. There is a strong need to develop a research capability for assessing the risks associated with medical devices and that is a priority item for the Agency.

   The existence of numerous variables which impact on performance requires that risk assessment for medical devices be accomplished in a manner individualized to the nature of the device problem. Problems in the manufacturing process, faulty products design, materials degradation and user errors are examples of the many variables which adversely affect the performance of a device or radiological product and result in a certain degree of risk associated with its use. Under these circumstances, risk assessment depends on which of the many variables are causing the problem. Minimizing the risk is dependent on the identification of an appropriate preventive strategy.

ACTION PLAN PHASE II INITIATIVES

At a minimum, FDA will undertake the following initiatives under APPII directed toward:

a. Improving the scientific base upon which risk assessments, and consequently risk management decisions, are made;

b. Reviewing the procedures associated with those scientific techniques;

c. Increasing public knowledge and critique of those activities;

d. Conducting regular peer review of risk assessment procedures to assess their validity and credibility; and

e. Striving to make public the basis of FDA's risk assessments through publication in the scientific literature so that the basis of governmental decisions can be clearly known.

Specific initiatives of the program, at a minimum, will be as follows:

Risk Assessment Research

To keep pace with changing technology through increasing knowledge of the biological mechanisms of diseases which result from exposure to toxic chemicals, each center will maintain risk assessment research programs coordinated through the Committee on Risk Assessment Research initiated in Action Plan Phase I. To achieve this:

a. Each center director, in addition to coordinating his own research program, will be responsible for preparing an annual report which details risk assessment research, collaborations with other centers, collaborations with external groups, and areas, both internal and external, where future collaboration would be useful. This report should include input derived from scientists' participation in the annual symposium described below;

b. There will be an annual symposium of scientists working on risk assessment research in FDA. A representative group of these scientists will form an organizing committee which will also be responsible for procedures to be used for selection of presentations; and

c. The committee will also be responsible for preparing an annual report to the Commissioner, describing achievements, areas of future promise and research needs.

Policy Development

In establishing policy, it is often useful to review procedures of the past. To this end:

a. Centers will review examples of their own representative risk assessments, whether formally recognized as risk assessments or found under a different title, to assure consistency of approach in its own processes, absent some justification for change or short deviation; and

b. Those reviews will be presented to the FDA Policy Board, after which a committee of the Policy Board will recommend procedures to improve the processes.

Public Understanding of Risk Assessment

Public education is an important aspect of the risk assessment program as a framework for understanding risk management. At a minimum, the following will be undertaken to achieve a better public understanding of risk assessment:

a. The Offices of Consumer Affairs, Public Affairs and Regulatory Affairs will develop programs to help the public understand that determining risks is an uncertain task, that scientific judgment is required to estimate risks, and that such judgment is limited by available knowledge;
b. FDA will also develop material useful in informing state and local governments of FDA's risk assessment approach and in providing educational material; and
c. The Commissioner and Deputy Commissioner will support an educational program coordinating these efforts.

Peer Review

Research projects conducted either intramurally or extramurally, whether or not they are in collaboration with academia and/or others, will have as an integral part, a peer-review process composed of the highest quality, unbiased scientists. The peer-review panel will be convened both for the review of research plans and the review of results.

Conducting Risk Assessments

The task force report to the HHS Secretary in April 1985 mentioned above, set forth general guidelines for the conduct of risk assessments. Based on that report:

a. Each FDA center will review each of the recommendations and develop implementation plans where appropriate; and
b. Each center's implementation plan will be reviewed by the FDA Policy Board to eliminate conflicting procedures.

Risk Assessment for Medical Devices

The area of medical devices represents an additional dimension to the commonly recognized, formal risk assessment process, and that area will continue to increase in terms of usage and medical impact. FDA, under the leadership of CDRH, at a minimum, will:

a. Delineate all of the components of a properly functioning risk assessment process for medical devices;
b. Develop a capability to gather device experience data (an important asset in the toxic chemicals area, not as readily available in the medical devices area);
c. Strengthen the medical devices research program to provide the increased knowledge necessary for more adequate risk assessment. This increase in the science base should include human factors engineering, materials science, electrophysics, and microelectronics; and
d. Improve FDA's access to medical expertise to ensure that experience data and laboratory based understanding of problems is tempered with medical judgment.

These important risk assessment initiatives will *significantly improve FDA's capabilities to carry out its regulatory responsibilities and materially contribute to FDA's continuing efforts to promote public health in a timely, effective, and efficient manner.*

9. HUMAN RESOURCES

FDA will devise, develop, and where feasible, implement programs designed to more effectively recruit, develop, and retain its most valuable resource, its people.

FDA's ability to prevent, identify, and resolve public health problems is dependent most heavily upon the skills and motivation of its employees—the Agency's most important asset. Approximately 65% of the Agency's budget is devoted to salaries and, therefore, represents the major resource investment of Agency appropriated funds. The majority of the remaining funds provides the equipment, buildings, supplies, and operating expenses needed to support directly the efforts of these employees. FDA's outstanding record of public health promotion and consumer protection, encompassing more than three-quarters of a century, could not have been possible were it not for the dedicated and hard working people employed at FDA. Then and now, the full range of employees—from the Commissioner through the Agency's entry level personnel—share common values including dedication to public service and dedication to timely, effective, and efficient accomplishment of the Agency's mission.

But many of the rewards associated with holding these values are intangible. FDA employees by and large are justifiably proud of the Agency's reputation, encouraged by the quality of their peers and motivated by the opportunity they have to contribute to the public's health. In recent years, however, the rewards of public service in FDA have been significantly offset by other factors and circumstances including anti-government rhetoric at all levels of society, over 10 years of resource reductions spanning several administrations, limitations on compensation, reductions in employee benefits, a lowering in the quality of work space and many other factors too numerous to list here. In spite of these factors and circumstances, however, FDA is fortunate in that, its work force has been relatively stable. Even this stability however, is contributing to a situation that if left unchecked, can lead to problems in the near future. *This situation is one of an aging workforce, long on valuable experience but close to retirement. New, younger recruits are not coming into the Agency in significant numbers.* In order to prevent further erosion of the current workforce from taking place, FDA must do all within its power to identify and change those practices that act as disincentives to employee recognition and to reward and to eliminate or substantially reduce the factors that decrease employee morale and performance. In addition, FDA must provide opportunities for its employees to make direct and substantial contributions that they feel personally responsible for creating—and support employee efforts to develop their knowledge, skills and abilities in order that each might achieve his or her "furthest star."

Under Action Plan Phase II (APPII), FDA will focus its efforts in the human resources area, at a minimum, on four major objectives:

1. Examination of FDA's personnel and management practices;
2. Recruitment and retention of FDA's scientific staff;
3. Development and training of FDA managers; and
4. Expansion of the successful Action Plan Phase I initiatives under the Commissioner's Advancement Program (CAP).

The first of these objectives will be a long term (18 months) initiative aimed at specific recognized areas of concern. The others will be carried out in the shorter term (6 months) and will be aimed at systematically identifying and overcoming barriers to employee performance and growth. A more in-depth discussion of each of these objectives follows.

Examination of FDA's Personnel and Management Practices

FDA will conduct an assessment of its personnel and management practices for the purpose of improving the quality of work life for Agency employees. The assessment will include identification of perceived and actual barriers in policy, procedure, rule, and law that prevent FDA employees and managers from maximizing realization of their potential for making contributions to the Agency. At the same time, a review of FDA's personnel and management practices will focus on identification of those positive practices that can be further promoted within the current system. The assessment will require a major, ongoing effort to identify both successful areas and problem areas and to institute timely change. It is within that context that a comprehensive and systematic review of these practices involving all levels of employees and management will be initiated including recruitment of new employees and special training programs. For this review to be successful, it must be both comprehensive in scope and responsive to current employee interests and needs. The approach will, to the extent possible, be modeled after the recent, successful comprehensive overview of FDA's medical device program conducted by several criticism task forces set up by the Agency's Center for Devices and Radiological Health (CDRH) during Action Plan Phase I. This initiative resulted in a clear understanding of what the true successes and problems were in that program. In turn, this made possible development of a realistic employee support plan to improve the Agency's device programs—based on well established facts rather than on unsubstantiated perceptions. Wherever necessary the internal review will be augmented by outside consultants both from government and from the private sector.

The Agency will build on the successes of Action Plan Phase I and on the CDRH criticism task force experience in the examination of FDA's personnel and management practices under APPII. Solutions are expected to range from short term policy or procedure changes (which can be accomplished within the constraints of existing authorities) through special demonstration projects such as those authorized under the Civil Service Reform Act.

The examination of FDA's personnel and management practices is sorely needed and is vital to the Agency's overall need to maintain its dedicated and highly motivated employees. While this comprehensive overview is being completed, several shorter term initiatives will be undertaken to better utilize current resources and thereby meet the Agency's ever expanding challenges.

Recruitment and Retention of FDA's Scientific Staff

For the Agency to timely, effectively, and efficiently carry out its regulatory responsibilities, FDA must maintain the highest scientific credibility. The most effective way to accomplish this is to attract and retain outstanding individuals with the necessary expertise and values. If supported adequately, such individuals in turn attract others, and eventually a pipeline is established to meet future needs. Biostatisticians are just one of many disciplines required for FDA's mission. The program outlined serves as an example of professionals on which FDA must concentrate its scientific recruitment efforts if the Agency is to be successful in meeting its future program needs.

To meet these objectives FDA will develop and implement a pilot project specifically designed to improve FDA's recruitment and retention of biostatisticians. A task force will be established to develop an implementation plan that will test new and innovative approaches to deal with FDA's difficulties in recruiting and retaining biostatisticians. The plan will include possible recruitment initiatives such as the establishment of direct hire authority, improvement of entrance level grades, and establishment of special pay rates; and if necessary to accomplish program objectives, development of legislative proposals and/or a demonstration project under the Civil Service Reform Act. In addition, retention initiatives considered will include the development of a model parallel career ladder which will enable biostatisticians to use a managerial option, or a research/expert option, for attaining higher level positions.

A companion effort to promote the scientific reputation of the biostatisticians occupational group throughout the world will also be developed. This promotional effort will be designed to foster extensive interactions with professional peers in academia and industry through multiple forums with the specific objectives of improving the recognition of FDA's regulatory mission and its scientific excellence. This will aid in establishing a recruitment network to assist in satisfying Agency recruitment initiatives in the future.

Employee retention is one of FDA's foremost concerns, particularly in scientific occupations where competitive pressures are producing high turnover and/or severe recruitment difficulties. This is particularly true in the cluster of scientific sub-disciplines included in biotechnology. Here, experience in FDA constitutes a major career opportunity. Therefore the Agency is experiencing an unusually high turnover rate. The issues to be addressed include, pay setting, professional recruitment, the sharing of the scientific accomplishments of the Agency with the scientific community, improving the image of the Agency with scientific peer groups, and providing career advancement potential for FDA's leading scientists comparable to that existing for managerial advancement.

Successful implementation of the pilot project would serve as a basis for other professional and nonprofessional groups in the future. Moreover, such an initiative could be implemented with little, or no negative programmatic impact, particularly in the long term since the projected outgrowth would be, at a minimum, a reduction in recruiting time to fill key positions as they become vacant. Optimistically, this effort could also produce significant program improvements such as better product applications. Any improvements resulting from these efforts to upgrade the recruitment and retention of FDA scientists would also have potential application to Agency employees more generally.

Development and Training of FDA Managers

Under the auspices of a Management Development Committee newly formed under APPII, FDA will conduct a study that includes: identification of the skills needed to be an effective FDA supervisor or manager; evaluation of how best to provide for the development of those skills; establishment of a program to greatly expand the lateral mobility of FDA's many quality managers at all levels through planned rotational details; identification and elimination of actual or perceived impediments to effective, efficient, and fair supervisory/managerial responsibilities; identification of existing and development of additional support systems to help managers reward their better performing employees and take positive steps to improve the performance of those employees who need extra effort; and development of proposals to best develop these skills in FDA employees who are likely to become supervisors/managers in the years ahead.

The responsibility for enhancing FDA's most valuable resource, its people, falls squarely on the shoulders of the Agency's first and second line supervisors. Most of these supervisors have had years of training and education in their particular field of substantive program expertise, but little, if any, training to prepare them for their responsibilities as leaders and motivators of human resources. FDA must train and develop Agency managers and focus their attention towards removing unnecessary impediments to providing more effective opportunities for the employees they manage. *A complete re-orientation of FDA's thinking in this regard is necessary.* FDA should encourage its supervisors to develop their human resources intensively, to facilitate productivity by the removal of barriers, to provide opportunities for lateral mobility, to reward and recognize those employees who are effective, and to hold accountable those who are not. The concept of pay for performance should be basic to the approach.

Expansion of the Successful Initiatives Under the Commissioner's Advancement Program

Under Action Plan Phase I the Commissioner's Advancement Program (CAP) advisory committee, chaired by Deputy Commissioner Norris and consisting of 19 FDA employees from throughout the Agency, was charged with providing the direction and management of various Agency training and development programs. The CAP advisory committee developed and implemented three successful employee advancement opportunities:

1. The Short Term Assignment Training (STAT) program, an intra-center or-office program aimed at providing focused career enhancement opportunities for GS-12 and above employees and PHS Commissioned Corps officers at all grade levels;
2. A pilot initiative for Project RENEW in the Center for Food Safety and Applied Nutrition, a center or office oriented program offering short term development assignments for selected employees. This is a self-identification program for employees at all grade levels who are performing satisfactorily or better, but who in the past 10 years have not participated in any type of substantive training, development or job enrichment activity; and
3. Project LIFE, a pilot program which supplements existing opportunities for obtaining college level training by assisting FDA employees in obtaining college credits for work experience.

Under APPII, these programs will continue and the RENEW program will be expanded agency-wide. The Project LIFE initiative will continue through its pilot phase and, if successful, will be expanded to a broader base population. Finally, the CAP Advisory Committee will investigate the feasibility of implementing, at a minimum, the following new FDA initiatives through appropriate mechanisms:

a. The appropriateness of three month sabbaticals to enhance productivity both for supervisory, as well as for non-supervisory employees, will be explored. Innovative alternatives will be considered which meet employee developmental needs and existing and future Agency requirements. The concept will not be restricted to opportunities outside of the FDA work environment. Many opportunities exist within the Agency to: enable the exchange of professional and managerial employees from one reviewing activity (e.g., CDB) to another (e.g., CDRH); provide fruitful new perspectives on programmatic approaches to problem solving; and broaden employee perspectives from a functional standpoint, while at the same time provide infusion of different thinking into existing management processes.
b. The CAP Advisory Committee, along with the FDA Secretaries Roundtable and the Division of Human Resources Management, will develop and implement a program designed to pay particular attention to the needs of secretarial and clerical staff—an extremely important and productive population within FDA. Such initiatives will include new and innovative recruitment approaches to satisfy the critical demands for personnel in this occupational group. In addition, since secretarial/clerical employees are in short supply and key to increasing the productivity of the Agency, it is incumbent that FDA pay particular attention to their developmental needs in designing these new recruitment approaches.

As these human resources initiatives unfold—the examination of FDA's personnel practices, the improvement of its scientific staff, the development and training of its managers, and the expansion of initiatives under CAP—all elements of the FDA employee population are to be dealt with equitably and fairly. FDA's plans and initiatives are *intended to support all employees, from the most modestly graded to the most senior managers; they are expected to address underrepresentation and career enhancement in all pay systems, including wage grade, general schedule, performance management review system (PMRS), senior executive service (SES), and Commissioned Corps. Finally, and possibly most importantly, FDA will include in these plans elements specifically designed to address the particular needs and concerns of women, minorities and the handicapped.*

10. INFORMATION, EDUCATION, AND TECHNICAL ASSISTANCE

FDA will expand its use of information, education, and technical assistance to prevent or resolve public health problems amenable to these approaches. Special emphasis will be given to public education.

Some of the public health problems associated with foods, drugs, and medical devices are caused directly by flaws in the products themselves, and are thus amenable to regulatory solutions (in combination with education and technical assistance) aimed essentially at correcting these products or removing them from the market. In other cases, however, the problem rests partially—and sometimes exclusively—with the *user* of the product: the health professional, the handler, the producer, the consumer, and the patient. Such problems encompass a broad spectrum of untoward events, including adverse drug reactions due to patient noncompliance, microbiological contamination of milk due to improper handling, and anesthesia injuries (90% of which have been attributed to either user error or problems in the user-machine interface). *These are problems linked more to people's behavior than to product characteristics, and a key to solving them is education—that is, a process of information sharing through which FDA alerts people to the problem and identifies its causes, and provides them with the knowledge they need to minimize or eliminate the hazard or to prevent its occurrence or recurrence.* In addition to using education as a means to deal with potentially hazardous products, the Agency also educates the public in a positive, preventive mode, as in its educational campaigns on sodium and cholesterol in foods, in patient education on the proper use of drugs, and in its ongoing efforts to keep health professionals and consumers informed about new developments and about ways to maintain and improve health. For these "people problems," education is frequently both the most efficient and the most cost-effective approach, and sometimes is the only approach, from a practical perspective, that has any hope of making a difference.

Although some FDA-initiated education may be considered "regulatory," in that it may stem from labeling requirements, many of the Agency's educational efforts go beyond such requirements—in informing health professionals and consumers, for example, and in cooperative efforts with state, local and foreign governments and with professional societies. FDA's scientific communication with health care providers and researchers through the professional literature comprises another important vehicle to transmit important public health messages. For example, data from several sources indicate that patient exposure to radiation from medical and dental x-ray examinations has decreased in recent years. Much of this reduction has occurred as a result of FDA research and FDA's education, via the professional literature, of clinicians and the radiology industry. And in the foods area, FDA has had major national impact using a multifaceted strategy of laboratory research to identify and characterize pathogenic organisms and modes of transmission, combined with education of the scientific, public health and manufacturing communities, as well as consumers (particularly those in high-risk groups).

FDA works extensively with private, nonprofit associations to promote public education. The Agency has provided background research to the National Council on Patient Information and Education to help them plan programs for patient education for prescription drugs. Similar cooperative efforts were conducted with the Pharmaceutical Advertising Council to jointly plan a campaign to combat medical quackery. FDA's support of education takes many forms. For example, it takes the form also of technical assistance and cooperative, information-sharing efforts with state, local and international health agencies, in which the Agency provides direct training, analytical resources, joint inspections, information exchanges, and FDA developed model laws and codes. A recent example is FDA's joint work with state and local agencies to combat microbial contamination of milk.

Education and information-sharing will assume increasing importance for the Agency in coming years. This is true for several reasons including:

a. In light of the veritable explosion in new medical technologies and the need to make them available as soon as possible, FDA's approval of new drugs and devices may become increasingly provisional in nature, with products deemed safe and effective only under certain limited circumstances and with indications and applications to be broadened as clinical experience increases. A recent example is the approval of a treatment IND for the drug AZT for use in patients with AIDS, in which the conditions for use were carefully circumscribed in advance. Under these conditions, it will be especially important both for physicians and for patients to understand and to be alert to the limitations, potential drawbacks, and precautions associated with the product. This includes the importance of their knowing which untoward effects need reporting and where to report them.

b. Beyond these specifics, health professionals and consumers (as well as the news media and the Congress) are becoming more aware that FDA approval of a product cannot be a guarantee of absolute safety or effectiveness. With this increased sophistication, and with more realistic expectations, there are also more questions. The public is increasingly interested in and demanding more information about the overall benefit-risk equations that underpin Agency decisions, and about the moral-ethical-societal issues involved. The artificial heart is a prime example. Thus there is a need for *general* education about risk assessment and risk management, and about how these tools are used in making decisions. A related need, particularly in the foods area, is education in *risk prioritization*, e.g., informing people about the relative magnitude of the risk of microbiological contamination of food versus that of food additives placed in food to control the former, but not without risks of their own. As the public grows to understand better that the world cannot be made risk-free, it is likely there will be an increasingly acute demand for information and advice about "ranking one's worries." Additionally, FDA will need to communicate to consumers how they can best protect themselves by proper use of products. It makes no sense to ensure that a product is designed and manufactured appropriately if user failures cause large numbers of major problems.

c. Because of the need to contain health care costs, the simplification and miniaturization of many medical products, and the trend toward patients assuming more responsibility for their own health status, the present tendency toward decentralization of health care will probably continue—much of what was formerly done in hospitals will be carried out in outpatient or extended care facilities, and home health care will play an increasingly significant role. Recent evidence of this trend includes the growing variety and popularity of home test kits, and the advent of sophisticated implantable drug delivery systems intended for outpatient use. This decentralization will require greater knowledge on the part of non-specialists—primary care physicians, medical support personnel and patients—and will heighten the need for FDA to educate these users. Additionally the increased number of elderly patients and the increased use of chronic, long term, therapies makes it imperative for consumers to have a more thorough understanding of the products they use.

Although there may be a growing *need* for education over the next few years, competing demands for Agency *resources* are likely to grow just as fast. Thus it will be vital to derive the greatest possible return from educational efforts through the husbanding of Agency resources. Several techniques, at a minimum, will be used to help maximize the impact of these efforts:

a. *Understanding Clearly at the Outset the Distinction Between the Product Component and the User Component of the Problem.* For example, in the case of eye infections among contact lens wearers, is the problem carelessness on the part of the user (which would lend itself to a consumer education solution), or is it something intrinsic in a particular lens material (which might call for manufacturer focused educational and regulatory solutions), or is it both? Even once a real public health problem is identified, such questions are frequently difficult to answer. But they must be addressed as the Agency seeks to determine the best and most efficient means to prevent or resolve public health problems.

b. *Targeting the Information at the Specific Audience That Needs It.* Although some of FDA's educational efforts, particularly in the foods area, must reach the public at large, many of the Agency's messages are better aimed at limited audiences. For example, when new questions arise about a drug used to forestall premature births, the target audience is primarily obstetricians and leaders and members of obstetric departments; when a cardiac defibrillator fails, this information should be focused on emergency medical personnel. To direct these messages in broad-brush fashion at the medical and public communities at large would be wasteful, confusing, and in the long run counterproductive, because people have a finite capacity to listen, to absorb, and to respond to such messages. In the prescription drug area, a segmentational analysis has been used to identify several methods by which consumers obtain prescription drug information. This analysis can lead to the development of separately focused but more finely targeted strategies to educate consumers.

c. *Repeating the Message to Be Sure It Is Received.* Since FDA does not provide "formal" education to product users and thus cannot control the circumstances under which people receive information, redundancy is essential in order to maximize the chance of reaching the target audience. The surgeon who should have new data on a cardiovascular product is more likely to receive it if it appears in several Agency announcements and professional publications than if FDA uses a "single shot" approach. Likewise, nutrition information for consumers and advice on how to avoid medical quackery can best succeed in changing behavior if they are repeated frequently and through many sources.

d. *Using Multiplier Groups to Help Spread the Message.* This is particularly important in making the best use of scarce resources. To ensure the dissemination of important information, FDA must capitalize on the existing communications networks of such groups as medical specialty societies, state, local and foreign health agencies, consumer groups, school systems, organizations of patients with particular medical conditions, industry groups, and the news media (perhaps the most potent multiplier of all).

e. *Using Innovative Communications Techniques.* To reach target groups with maximum timeliness, effectiveness, and efficiency, it is vital to capitalize on new technologies that can help to transmit the Agency's messages swiftly and clearly, yet at minimum cost and effort. For example, a new and highly successful technique to communicate with professionals attending national meetings has combined the showing of a previously videotaped interview of FDA personnel during a meeting with a subsequent "live" conference call during which the FDA employees answer questions from the floor.

f. *Gaining Early Input From Professional, Consumer, and Health Organizations in the Development of the Message.* Gaining early input from special interest groups is often vital to assure the cooperation of these organizations in: (a) developing the message, to help insure accuracy and relevance; (b) disseminating the message, to be sure that the organization's constituents will find out about it; and (c) endorsing the message, to increase the likelihood that these constituents will act on it.

g. *Directing Education and Information Messages to Populations Not Normally Reached by Traditional Dissemination Techniques.* It is important that health alerts and education programs be directed to all population segments including those who do not get their information from the mass media. FDA will, therefore, work with organizations which represent these populations and develop special education programs to reach them.

h. *Understanding the Informational Needs and Potential Effects of Any Educational Strategies Undertaken.* Thoroughly researching educational problems and investigating the potential for certain messages, channels, and targets for communications will help assure that educational goals are more fully attained. General knowledge drawn from professional literature and consultations with experts as well as specific research and analyses can aid in understanding and predicting the effectiveness of communications.

Taking into account these "maximizers," the following are examples of significant educational initiatives that, at a minimum, will be undertaken and completed by FDA to address public health problems over the next 6-18 months, the time frame of APPII.

Tampering

To minimize the effects of tampering crises, should they occur again, the public needs to know how to avoid tampered-with products. The Agency will work with over-the-counter (OTC) drug manufacturers to stress what people can do to recognize tampered-with products, and will work with trade groups to educate the public about the criminal provisions of the anti-tampering law.

Safe Practices in Kidney Dialysis

There are now more than 78,000 patients with end-stage renal disease receiving ongoing dialysis treatment. It is known that the techniques used by the health care personnel responsible for these treatments can affect patient morbidity and mortality. FDA will work with professional groups, manufacturers and standards organizations to identify and characterize the use problems associated with dialysis and to develop educational programs to improve the performance of dialysis practitioners.

Drug Residues in Livestock

Despite the Agency's extensive past efforts to correct the situation, illegal drug residues in livestock resulting from improper use of animal drugs remains a significant problem. FDA will expand its existing educational program in this area, which is geared to specific producer groups, veterinarians and other segments of the agribusiness community. The educational message, to be disseminated in conjunction with appropriate regulatory activities, will stress the importance of using only approved drugs, and then only for approved applications, and only at approved levels.

Microbiological Contamination of Milk

Several recent outbreaks of milk-borne disease have caused heightened concern about microbiological contamination of milk and milk products. To help prevent future incidents, FDA will conduct a cooperative program with the states and the dairy industry which will intensify surveillance of sanitary conditions in processing plants. Included will be advice to states and industry on improving quality control and training on advanced dairy processing. These information education activities will be carried out in conjunction with an increased number of joint state—FDA evaluations of pasteurization plants and a sampling program for specific micro-organisms.

Chemical Contamination of Foods

With considerable national attention focused on chemical contamination of foods, and with several agencies responsible for various aspects of the problem, it will be increasingly important for FDA to coordinate its activities with these agencies in order to avoid duplication and inconsistency. FDA will place increased emphasis on improving coordination with USDA and EPA, to assure more uniformity and agreement in tolerances and residues, in communications with the states, and in joint projects and emergency responses.

Health Fraud

It is estimated that health fraud, the promotion of false or unproven products for profit, costs consumers up to $40 billion each year. In addition, it exposes them to direct and indirect health hazards, many of them major. When fraudulent products pose a direct hazard to health, immediate enforcement action generally is appropriate. In other cases, where the adverse effect on the consumer is mainly economic, educating the public is frequently one of the best preventive strategies. FDA's successes in this area under Action Plan Phase I are delineated in the Foreword to APPII. They include: holding three regional health fraud conferences; sponsoring a National Health Fraud Conference in Washington, D.C.; holding health fraud conferences with local coalitions in each of FDA's 21 districts; issuing a joint alert with the Better Business Bureau on weight reduction practices; developing a public awareness campaign with the Pharmaceutical Advertising Council; and conducting a Hispanic Health Fraud Conference. FDA therefore will continue and expand the strong initiatives undertaken in Action Plan Phase I by working with other organizations to form coalitions (as well as to build on existing relationships) which are aimed at sharing information and at providing consumers, health professionals and the news media with the information they need to avoid health fraud. For example, FDA is planning for a second National Conference on Health Fraud in early 1988. The Agency is also planning a National "Ask the Expert Day" with Call For Action, Inc. and the Arthritis Foundation. In addition, FDA will continue the public service campaign conducted jointly with the Pharmaceutical Advertising Council and continue to facilitate the expansion of the Information Exchange Network developed by the National Association of Consumer Agency Administrators.

This renewed *focus on information, education, and technical assistance within FDA should significantly enhance consumer protection by helping the user of FDA regulated products—the health professional, the producer, the distributor, the consumer, and the patient—understand more about the causes of problems and by providing them with the knowledge they need to minimize or eliminate the hazard or to prevent its occurrence or recurrence.*

11. COMMISSIONER'S SPECIAL INITIATIVES

Recognizing that, because of their broad-based organizational nature, the first ten goals do not address certain specific substantive areas of specific concern, the Agency will undertake, under the leadership of the Commissioner, special initiatives for Women's Health, Science, Orphan Products, and Technology Assessment and Transfer—areas that the Commissioner has specifically selected for added focused efforts.

In the ten goals for Action Plan Phase II (APPII) articulated in the preceding sections there has been a plan of action put forth to address many of the Agency's major concerns. Most of these have been strongly program specific. The Commissioner has determined that four additional issues, of a more crosscutting nature, should be addressed. These initiatives will carry the three themes of Health Problem Identification, Health Problem Prevention, and Health Problem Resolution, to address FDA's concerns with enlarging the women's health efforts, improving scientific capabilities of the Agency with a special emphasis on biotechnology, expanding efforts in support of orphan products, and facilitating technology assessment and transfer.

APPII INITIATIVES FOR PROTECTING AND PROMOTING WOMEN'S HEALTH

Society has changed dramatically during the twentieth century and, attendant with this change, women have experienced the opportunities and demands of new roles, different expectations, and more diverse choices as well as the added stress accompanying rapid changes in family dynamics and concomitant modifications in society. Varied lifestyles and expanded opportunities, societal changes of family dynamics, and a shifting national demographic profile are key factors which have converged to illuminate the spectrum of health problems confronting women and the need to reassess women's health within the context of the lives they lead today. Medical, technological, and scientific research has afforded society, its institutions, and women themselves with a sufficient knowledge base for addressing the health problems impacting on women through informed health management. In addition, women have come to take a strategic part in health care in the United States through their role as custodians of the family health care system. This role is expected to become increasingly important as health care becomes more decentralized to the outpatient setting.

As a public health agency, FDA is keenly aware of the significance of its responsibilities and programs to the status of women's health within the United States. Encouraging the development and availability of products beneficial to women's health as well as resolving the product problems that may endanger women's health are key elements of FDA activities in such areas as premarketing review, labeling, risk assessment, risk management, and product postmarketing surveillance. Through its program operations on the national and local levels, the Agency addresses those health concerns that impact on women exclusively, predominantly, or differently from men. These activities, aimed at developing and promoting information to assist women, their health care providers, and industry, include the following:

a. Education and technical assistance programs in such areas as drugs and their use during pregnancy, special concerns of women exposed to medical radiation mammography and scoliosis examinations, and the relationship of toxic shock syndrome and tampon use;
b. Scientific research directed to developing ovarian toxicity screening methods, kinetic approaches for the treatment of pre-term labor, and diagnostic ultrasound;
c. Studies and data analysis in such areas as the long-term effects of drugs, the nutritional management of infants with low birth weight and birth defects, and the Toxic Shock Syndrome Active Surveillance Study; and
d. Major program activities related to the prevention and treatment of osteoporosis and the development of approaches for communicating information to health care providers.

These sustained activities have provided the Agency with long-standing constituencies in both the public and private sectors that are committed to improving women's health and that form an essential resource for expertise, participation, and education about women's health.

A major milestone in assessing the status of women's health in the United States involved a two-year, nationwide study conducted by the Public Health Service (PHS) Task Force on Women's Health issues (now the PHS Coordinating Committee on Women's Health Issues). This study, commissioned by the Assistant Secretary for Health, represents a comprehensive review of women's health, the factors impinging on those conditions of health and well-being, and specific recommendations for actions that can be taken by government, the public health community, and other sectors of society to improve the status of women's health.

As a member of this Task Force, FDA continues to recognize that the maintenance of good health is a societal as well as an individual responsibility and strongly endorses a collaborative approach to addressing the health problems impacting on women and to providing the information needed to assist them in adopting good health practices. Many of the risks associated with major serious disease conditions affecting the health of women can be minimized or completely eliminated through the intervention of early disease prevention and health promotion behaviors. Lung cancer, breast cancer, stroke, hypertension, osteoporosis, and urinary incontinence, all represent potentially debilitating conditions that can be controlled in varying degrees through informed health strategies. Keeping the public, particularly women, involved and informed about matters of health and well-being together with a heightened emphasis on disease prevention and health promotion can provide a significant source of information and encouragement to women, as well as facilitating longer term benefits.

In carrying out the recommendations of the PHS Task Force on Women's Health Issues related to its mission, FDA has made a substantial commitment to improving the status of women's health as part of the nation's overall goal of enhancing the health of all people. Guided by the findings of the Task Force, FDA and the PHS Coordinating Committee on Women's Health Issues, joined efforts to provide a national forum for assembling recognized experts in various disciplines relating to women's health. This forum was designed to present a baseline of medical and scientific information on key women's health concerns. This conference was a first effort to bring together the diversity of the public health community to focus national attention on women's major health problems and to establish the foundation for future collaboration to incorporate the information presented at the conference into educational messages for community programs. The 51 expert panelists and 650 conference attendees constitute the core of an informed and active constituency within the public health community with an expressed commitment to improving the status of women's health through such diverse initiatives as research, innovative technological and product development, hospital and community health care and services delivery programs, health information and education programs, and medical practice and patient counseling.

To bring about a consolidated and focused women's health effort within the Agency, Commissioner Young established an internal advisory group, composed of representatives of the FDA Policy Board with members from each FDA component, to advise and assist him in directing and managing the FDA response to women's health issues within the context of the Agency's mission and responsibilities. In meeting its responsibilities, the FDA Advisory Group on Women's Health Issues instituted a process for identifying priority women's health concerns and for developing effective approaches for addressing these concerns. The Advisory Group assembled agency-wide working groups whose members possess relevant expertise and skills to study key cross-cutting women's health issues, to make specific recommendations regarding possible Agency actions, and to manage agency-wide participation in carrying out selected actions. It has also established an Education Subcommittee to recommend how health information can best be made available to women and to encourage them to incorporate this information into their personal health care practices.

As one of the Commissioner's Special Initiatives under APPII, women's health will be further reinforced as an identifiable public health priority for the Agency and serve as a national focal point for building the cooperation and incentives needed to inform women about their health and to assist them in practicing effective and beneficial health behaviors. This special four-part initiative will, at a minimum, include FDA's:

1. Identifying priority public health problems with a particular impact on women; developing workable approaches for addressing these problems in collaboration with the public health community—the research and medical communities, government, industry, consumer organizations, women's health groups, health-oriented community organizations, public health educators, and the media;
2. Conducting national forums, and special workshops to establish a baseline of medical and scientific information on key women's health concerns and to facilitate the development of educational messages for community programs;
3. Developing the network and resources needed to sustain and expand the exchange of information among active, informed constituencies in both the public and private sectors; and
4. Increasing a national awareness of women's health problems and the materials and methods that can be used to support women in their efforts to be healthy.

This special initiative will *significantly improve the ability of women to help in their own health protection efforts and represents FDA's continuing high priority attention to the special health needs of women.*

APPII INITIATIVES FOR IMPROVING FDA's SCIENTIFIC CAPABILITIES

This is an age of monumental scientific discovery and technological innovation. Though scientific information is constantly evolving, the need to protect the public health remains a constant, unflagging concern; one that is, of necessity, based on this expanding foundation of science.

FDA, in its consumer protection role, for only $1.85 per American, has the regulatory responsibility to protect the health of the American public by assuring the safe entry and retention in the marketplace of some $550 billion in products. In carrying out its responsibilities FDA occupies that vast region between the border of scientific discovery and the marketplace of products. The cornerstone of FDA's activities for public health protection is its scientific personnel and unique research capabilities. FDA scientific activities have several characteristics which make them unique among scientific institutions including:

a. Research is often specifically focused on questions related to FDA's oversight of regulated products. This type of research is not found elsewhere in government;
b. Research is often directed toward solving life-threatening public health problems that constitute emergencies such as product tampering and food poisoning;
c. Scientific and risk assessment information that is FDA product-related serves as unique disease prevention information when utilized by industry, consumers, and other federal and local government agencies;
d. Research and scientific activities are the foundation for Agency regulatory actions. These scientific activities allow the Agency to function as a unique gateway in the transfer of new technology to the marketplace; and
e. Accurate methods developed by research and validated through application serve FDA's compliance and enforcement programs.

Unlike the basic biomedical research supported by NIH and NSF, FDA's research is, in part, aimed at providing information specific to the Agency's mission. The research undertaken by FDA, NSF, and NIH is in fact, complementary: FDA takes information suggested by basic research and applies it to national public health needs. However, unlike most basic research which may come to fruition years down the road, it is gratifying and exciting for FDA scientists to see the outcomes and benefits of many of their research efforts more quickly, for example, in the form of new product approvals or seizures of dangerous products.

An advantage for the investigator in FDA's research enterprise is that it provides an interesting mix of research activities: basic research that complements studies in academia and NIH and "applied research" focused on a particular product or product-related problems of intense national need.

Because of its broad regulatory responsibilities, FDA must maintain expertise in many diverse scientific areas including biology, chemistry, microbiology, pharmacology, toxicology, engineering, and physics. Scientists with expertise in these areas undertake the basic and applied research which then forms the basis for many of FDA's regulatory activities. FDA's unique research areas are described below:

a. *Product Testing and Review of New Product Applications.* The responsibility for ensuring that the products FDA regulates and approves for marketing are safe and effective rests with the scientists who review the product applications. To make sensible regulatory decisions about new products or processes, FDA scientists must have in-depth knowledge, gained through hands-on research experience. The Agency requires a unique type of M.D. or Ph.D. scientist as a product reviewer. Many are bench scientists who perform basic research and who apply the same scientific expertise and judgement to new product application. For example, scientists in CDB doing virology research related to vaccine development are also those who review the applications for new vaccines. Similarly, those scientists in CDRH who conduct research to facilitate improvements in the design of prosthetic heart valves perform premarketing reviews of new heart valve designs. These scientists with expertise in the field that will be regulated are equipped to make more expeditious and informed decisions. Some FDA scientists are also involved in research that will lead to the development of new products. Research on a pertussis vaccine with fewer side effects is taking place in CDB. Scientists in CDRH, in collaboration with Duke University, have developed a more sensitive ultrasound imaging system, thus reducing the possibility of overexposures. Also, CDB scientific research was instrumental in the development of the HTLV III (AIDS) antibody test kit.

b. *Hazard Determination.* To ensure that the food supply is safe and wholesome, some FDA research is focused on the identification of contaminants which could pose serious health hazards. The recent serious outbreak of listeriosis from contaminated dairy products illustrates several of the features which make FDA science unique: it is research unlikely to be done at other institutions; it is research directed toward solving public health emergencies; and it provides scientific information necessary for disease prevention. Research by CFSAN scientists resulted in tests to differentiate pathogenic and nonpathogenic strains of Listeria. When the listeriosis outbreak in California required an immediate survey of domestic cheeses, FDA scientists developed a selective medium to enhance the detection of the organism among all the other microbes found in dairy products. This method has been adopted by industry and foreign governments to monitor dairy products and to prevent a recurrence of Listeria contamination. Continuing research is attempting to improve further detection of Listeria and other important pathogens with specific DNA probes.

   A second example of research to support hazard determination is CDB research which resulted in the development of a reliable *in vitro* assay to detect bacterial endotoxin in human pharmaceuticals, an assay which is widely used by industry.

c. *Development of New and/or Improved Physical, Biological, Toxicological or Chemical Tests*. FDA scientists must often devise or improve tests to ensure comprehensive evaluation of products from new technologies. For example, CDRH scientists have recently designed special ultrasound transducers which are used in a novel laboratory system to characterize the flow pattern of blood through prosthetic heart valves. This test system will be used to evaluate new heart valves developed by industry.

d. *Determination and Establishment of Standards and Determination of Product Compliance With Those Standards*. Industry and state governments rely upon FDA to develop and set standards for the products it regulates. These standards set a level of purity for drug and food products or define the performance of certain medical devices. For example, CVM scientists have developed analytical methods to detect very low levels of aflatoxin, a natural contaminant of foods, so that the aflatoxin standard can be enforced. In CDRH, scientists have devised the test methods needed to develop standards for x-ray machines, thus reducing unnecessary radiation exposure.

e. *Clarifying Mechanisms Underlying Toxicologic, Biologic and Pharmacologic Effects*. Risk assessment research at FDA is critical to the rest of the Agency's regulatory activities. It underlies the basic questions about the human health implications of all the products FDA regulates and is thus related to much of FDA science. At NCTR, research is undertaken to validate or adjust appropriately many of the assumptions upon which risk assessments are based, to reduce the uncertainty and increase the accuracy of the risk assessment process. NCTR collaborates with the rest of FDA's centers to address their specific risk assessment needs (e.g., identifying biomarkers to estimate risks from chemical carcinogens, or developing estimates of risk to humans from device failures and the concomitant impact of those failures on health care delivery).

f. *Supporting Developing Technologies*. While scientific and technical knowledge in the biomedical sciences relies most heavily on the support of the NIH and NSF, FDA has a critical role to play in assuring that products of new technologies reach the marketplace. The role of FDA is particularly evident in the areas of biotechnology and innovative medical technologies. For example, advances in molecular biology and immunology over the past 25 years (e.g., gene splicing, cell fusion, DNA sequencing) have resulted in products now ready for commercialization. FDA scientific expertise in these new technologies has been essential to developing a reasonable regulatory approach toward and to the evaluation of these products for safety and efficacy. As a result, numerous biotechnology products have been approved by the Agency in the last several years including close to 200 *in vitro* diagnostic kits utilizing monoclonal antibodies, a dozen diagnostic DNA probes, and 6 important recombinant DNA-derived drug products such as human insulin, human growth hormones, alpha interferons, and a Hepatitis B vaccine. Equally important approvals in the medical device area have facilitated the commercialization of other cutting edge technologies (e.g., medical lasers, microelectronics, new materials for biomedical use).

Clearly, FDA's scientific activities provide a foundation for the Agency's regulatory mission of protecting the public health and, as FDA looks toward the future, the Agency must reflect upon its increasing responsibilities in light of the current fluid scientific environment.

How can the Agency continue to safeguard the public health in the face of increasing uncertainty prompted by constant scientific and technological change? Clearly, one of the most obvious ways to ensure that FDA can meet the demands of scientific change is to continue to employ the most highly qualified scientists.

Thus, FDA will address three areas under APPII which focus Agency attention on sustaining or enhancing its scientific capabilities through its scientists by, at a minimum, creating:

a. Enhanced recruiting and retention efforts for scientists of the highest possible calibre;
b. Increased visibility and support for Agency science and scientists; and
c. Increased efforts to enhance communication by FDA scientists on scientific and technical issues.

The specific APPII initiatives to improve FDA scientific capabilities will, at a minimum, include the following:

Recruiting and Retaining Scientists

The scientific wealth of the Agency resides in its scientists. How then, can FDA attract and keep top notch scientists who have a commitment to public health and who are interested in pursuing the basic and "applied" regulatory research the Agency needs? The need to recruit young scientists is becoming more acute as an increasing number of FDA scientists retire or move to industry. In fact, a recent Agency study indicated that the average age of the FDA scientist to be 44 years.

In addition to attracting premier scientists, FDA must undertake efforts to keep and nurture those scientists. How can FDA provide a working environment in which scientists can actively pursue their scientific interests as well as fulfill the regulatory responsibilities of the Agency? Goal 9 of APPII describes several initiatives to address FDA's overall human resource concerns. To highlight the special needs of the Agency's scientific staff, however, the Commissioner's special initiatives on science will supplement the Goal 9 objectives relating to scientific staff. Using microbiologists as a paradigm, additional issues regarding recruitment and retention of Agency scientists will be addressed. Microbiologists are essential to the activities of each center and of the field laboratories. Biotechnology is one example of a technology based in microbiology that affects all parts of the

Agency and for which microbiological expertise is required. In CFSAN, "food microbiology" has evolved from an operation merely to identify and count microbes in food. The long list of microbiological concerns, the presence of pathogens in highly perishable products, and the increasing complexity of pathogenic mechanisms has dictated that FDA adopt the most current technologies and apply them to emerging problems in food safety. Microbiology has similar importance in other centers, from AIDS and new vaccines in CDB, to antibiotics in animal feeds in CVM, to the development and approval of gene probes in CDRH, and to the development of microbial detection assays in field laboratories. Various initiatives, described below, will be considered along with those developed in Goal 9. FDA, under the leadership of the Commissioner will, at a minimum, undertake specific *recruitment* initiatives, including:

a. Develop an assessment of current and projected FDA scientific needs and the particular skills needed to address those needs;
b. Encourage scientific managers to interpret and set the scientific grade levels based on their particular scientific needs;
c. Develop a recruitment brochure for microbiologists;
d. Continue to develop relationships with universities, medical schools and scientific societies as possible recruiting networks;
e. Explore the establishment of an honorary "chair" in microbiology to increase the prestige of particular research in that area; and
f. Increase the funding of FDA postdoctoral training programs targeted to microbiologists.

Additionally the Agency will study the possibilities of establishing a direct hire authority for microbiologists and providing special pay rates or improved entrance level pay grades so that FDA can compete for scientists with industrial and academic pay scales.

FDA will also undertake specific initiatives *intended to retain the outstanding scientists currently working in the Agency*, including:

a. Conduct a study or perform exit interviews to determine why microbiologists are leaving the Agency;
b. Develop a plan to assure that quality scientific work is recognized through promotions (including developing career ladders that specify advancement opportunities, developing peer review systems for similar positions across the Agency, and enforcing parallel goals and levels of achievement between individual peer review evaluations and formal performance measuring systems);
c. Develop work performance goals which are achievable and do not unfairly impede scientists (e.g., lab safety);
d. Develop a mechanism for FDA to participate in Stevenson-Wydler initiatives;
e. Develop a sabbatical program for qualified microbiologists to enhance and reward distinguished research; and
f. Support attendance at scientific meetings by establishing special funding for participants and presenters.

Successful implementation of these initiatives will serve as the model for other groups of scientists in the future.

Building of Science

FDA scientists face circumstances which make the job of regulatory science more complex than ever. They have to respond to pressure from several diverse sources such as Congressional policy-makers and informed consumers demanding definitive answers to questions of health and safety risk and requesting more information on product risks and from industry itself, requiring FDA scientists to be conversant with the latest information and technological developments in widely disparate disciplines. To meet the challenges of such a changing environment, FDA must assure that science remains dynamic. One way to assure that the FDA scientists can meet increasing demands is to provide a work environment that recognizes, nurtures, and promotes scientific excellence. Scientists must feel that their work is respected, valued, and that they are intellectually stimulated, and encouraged to be creative in their scientific endeavors. Laboratory research should be regarded as the primary activity of many FDA scientists and in no way secondary to other regulatory activities. There is just no substitute for outstanding scientists.

The concept of the "scientific environment" is elusive but relates to many different components of the Agency: the relationship between scientists and management; the condition of the physical plant, including laboratories, libraries and equipment; the level of administrative support for scientists with a focus on removing administrative barriers; and the degree to which intellectual needs are satisfied.

The total scientific environment reflects the perspectives of three components: that of the Agency, the center, and the individual scientist. The individual scientist needs to feel that he or she is an integral part of the mission of the center, that his/her work is exciting and important to the Agency and that a sense of *esprit de corps* with fellow scientists exists; each center needs the team efforts of all its scientists and non-scientists to accomplish its particular goals; and the Agency as a whole relies on the smooth interactions and collaboration of all centers to accomplish its regulatory mission.

The scientific strength of the whole Agency is the sum of the strengths of each individual scientist. With that in mind, the Commissioner and top management of FDA are firmly committed to developing a scientific environment within the Agency that visibly supports scientific personnel and that actively promotes excellence in scientific endeavors. To develop mechanisms which contribute to a positive scientific environment within FDA and which are tailored to the needs of individual scientists, the centers and the Agency alike, the following initiatives will be undertaken:

a. The Commissioner will review, with the center leadership, the scientific programs in each center and in the field through a series of comprehensive briefings;
b. Scientific focal points will be identified for each center and the field, and where appropriate, a plan of future scientific activities devised; and
c. The Commissioner and his Coordinating Council will provide the review and oversight of these plans to assure the Agency's scientific needs are being met.

The purpose of these initiatives will be to assess the scientific programs throughout the Agency and to ensure that a supportive scientific climate for accomplishing Agency goals exists within those programs.

The following are suggested mechanisms which will be considered to further improve the scientific climate in the Agency:

a. Establish a criticism task force to determine the positive and negative aspects of FDA's support of scientific endeavors;
b. Review the types of tracking and reporting systems management requests of scientists. Eliminate those which are duplicative or unnecessary and simplify those that are overly burdensome. This will enhance the stability of the work environment which tends to change with new Commissioners or management styles;
c. Determine if the stability of the scientific environment could be enhanced by developing a "special initiatives" fund to support one or two research programs of broad public health significance for 2-4 years;
d. Streamline procurement procedures for lab equipment and supplies;
e. Encourage increased administrative support to the scientific staff by emphasizing problem-solving as the bottom line, with less emphasis on the process used to get there;
f. Coordinate budget and planning cycles to allow research to dictate budget needs and projections of potential personnel needs;
g. Develop mechanisms which encourage Agency scientists to improve their skills or keep up with technical innovations (e.g. continuing education, sabbaticals, training opportunities, etc.);
h. Increase the visibility of the Sigma Xi Chapter in FDA to support excellence in research;
i. Encourage publication in peer reviewed journals; and
j. Explore establishing an FDA edited journal.

Exchange of Scientific and Technical Information

The exchange of scientific and technical information by Agency scientists about FDA scientific and policy issues is critical for maintaining FDA's strong technical leadership. This increased need for communication stems from the explosion of scientific and technical information scientists must be familiar with in order to make decisions based on the currently acceptable state-of-the-art. Developing mechanisms which facilitate an exchange of scientific-technical information is one way of sustaining and improving the scientific capabilities of the Agency.

General initiatives to facilitate scientific-technical information exchange are needed in three areas:

1. Improving the channels of information *within* FDA;
2. Access of FDA scientists to information *outside* the Agency; and
3. Dissemination of certain scientific and regulatory information *from* the FDA.

Three APPII initiatives to address these concerns are:

1. A directory of FDA scientists will be developed and will include a 250-word abstract from each scientist describing his/her research and regulatory interests. The research abstracts will then be cross-indexed by key words. This is critical to strengthening the scientific linkages throughout FDA in information which describes the scope of Agency scientific expertise;
2. FDA will increase scientific communication and technical information exchange among FDA scientists and provide a visible means of support for Agency scientists through a Commissioner's Scientific Seminars series. The Commissioner will sponsor scientific seminars highlighting the research of noteworthy FDA and non-FDA scientists. Opportunities for scientists to discuss issues with the Commissioner will follow each seminar; and
3. A weekly calendar of events will be published listing all FDA seminars, symposia or guest speakers for that week.

All of these relatively simple but important efforts will provide mechanisms to encourage and facilitate the flow of information among FDA scientists. Other suggested activities that will be considered include establishing a scientific electronic bulletin board or consolidating data/information bases. For example, a survey of existing scientific data bases might assure that these are accessible, where appropriate, to all Agency scientists and that they are used in the most economical way possible. Some consideration should be made to standardize information included in these data bases to facilitate their use by all scientists throughout the Agency and eliminate duplication. There has also been some interest in developing centrally searchable literature data bases for cross-cutting FDA issues which would save search time and the added cost of duplication.

Access to information outside FDA will be increased through established staff exchange programs, mini-sabbaticals, other means of professional development (e.g., membership in scientific societies and presentations at scientific meetings) and mechanisms to encourage collaborations between FDA and non-FDA scientists.

These initiatives will *sighificantly improve FDA's scientific capabilities and will better position the Agency to apply the best science in developing regulatory approaches and in making regulatory decisions.*

APPII INITIATIVES FOR FACILITATING ORPHAN PRODUCTS AVAILABILITY

FDA has had a long history of facilitating orphan product availability to patients with rare diseases and conditions. Such products, being by definition of limited commercial value, need FDA's assistance to obtain sponsors to manufacture and bring them to market. In 1982 realizing that more focused Agency action would result in enhanced orphan product availability, the Commissioner formed the Office of Orphan Products Development in his immediate office to facilitate the development and availability of needed medical therapies for patients with rare diseases.

On January 4, 1983, President Reagan signed the Orphan Drug Act which, among other actions, added four amendments to the Federal Food, Drug and Cosmetic Act to provide new incentives to sponsors for the development of orphan drugs. Through designation of drugs as orphan products eligible for expedited review and for financial grants for clinical studies, the Agency has additional tools to make needed drugs like Trientine for Wilson's disease and L-carnitine for genetic carnitine deficiency available to the several hundred patients who desperately need them.

With increasing availability of such drugs, a special initiative on orphan products is needed if the increased availability of such drugs is to be made meaningful and to continue.

Information and education are the primary elements in the initiative to assure that (1) doctors and patients are able to access information about rare diseases and available therapy, (2) researchers developing innovative therapeutic ideas are made aware of FDA's clinical grant program as one resource to assure that such ideas do not languish for lack of development capital, and (3) leaders of government and science are made aware of FDA's special place in assisting technology transfer from basic research to approved therapies from both intramural and extramural efforts.

FDA will intensify its educational program to government, industry, academia, health professional organizations, voluntary organizations, and international regulatory authorities so that they will be aware of the Agency's activities in orphan products development. Such knowledge should foster the investigation of new orphan products and assure the appropriate use of newly approved orphan products.

Commissioner Young and Deputy Commissioner Norris will highlight for Congress FDA's accomplishments and needs in orphan products development. They and their staffs will make presentations to the *National Commission on Orphan Diseases* to describe FDA's unique role in product development and availability with special emphasis on FDA's grants program and intramural research. They will do the same to industry, assuring that intensified interaction with the *Pharmaceutical Manufacturers Association Commission on Drugs for Rare Diseases* will take place to identify specific problems, such as product liability as a barrier to orphan product development, and to obtain a consensus approach to problem solving. Grants to researchers in academia, medical practice and industry will continue to be awarded, and increased technical assistance will be provided to the principal investigators to maximize the yield from such research. The staff will increase the number of articles, presentations, and personal interactions involving health profession organizations, voluntary groups and international regulatory authorities on FDA's orphan product development program to increase awareness of approved orphan drugs as well as those in development.

The composite effect of these educational efforts will *be to increase awareness and understanding of FDA's orphan products development program so that emerging new treatments for patients with rare diseases will continue to be made available on a timely, effective, and efficient basis and will be appropriately utilized to maximize realization of their potential benefits to the health of these patients.*

APPII INITIATIVES TO FACILITATE TECHNOLOGY TRANSFER

A bipartisan effort by the Administration and Congress culminated in 1986 with the enactment of the Federal Technology Transfer Act of 1986. This legislation is intended to improve the transfer of commercially useful technologies from the federal laboratories into the private sector. It is based on the premise that international competition has forced the United States to use all technological resources available.

In 1960, the United States enjoyed 21% of the world's trade; that was down to 14% in 1985. Also in 1960, the United States enjoyed a $5 billion trade surplus compared to a $170 billion trade deficit in 1986. The United States sold $24 billion more in technological items than it bought in 1981. That margin was down to $5 billion in 1984. Superimposed upon these facts is the widely held belief that technology is the engine that will drive future economies.

A number of countries around the world are increasing their efforts in technological innovation. In spite of the worsening position on international competitiveness, the United States has continued a dominant role in technological innovation. Of 500 seminal technological breakthroughs from 1953 to 1973, 63% were made in the United States. Japan, one of the leading competitors made 5% of the breakthroughs.

The legislative history of this legislation indicates there was widespread concern over the fact that so few technologies were commercialized out of a substantial resource within the federal sector. There are approximately 700 government laboratories spending about $18 billion per year. That resource represents one-fifth of the nation's laboratories and equipment and one-sixth of the nation's scientists. Yet, less than 5% of 30,000 government patents have been developed into products. Testimony presented arguments that restrictive patent laws have prevented commercialization by U.S.

firms, but not by foreign firms. It was found that frequently foreign firms patent the technology developed in the U.S. and sell the products back to this country, increasing the trade deficit.

Among other items, the Technology Transfer Act provides the opportunity to enter into cooperative research and development agreements with industry, individuals, universities, state and local governments, and others. Through those agreements, it provides the opportunity to accept funds, personnel, services, and property while providing all of those resources in return with the exception of funds. Furthermore, it provides for the opportunity to grant patent licenses, to waive non-exclusive licenses, and to permit employees to commercialize inventions.

FDA recognizes the need to do its part in support of this important legislation. In addition, the Agency sees a significant opportunity for the protection of public health through fully embracing the possibilities within this legislation.

The explosion of the techniques associated with molecular biology, first from the academic community into private industry, has every opportunity for continued significant growth. Forecasters have indicated that small business has picked up that trend and will continue to develop products based on new scientific discoveries whose practical applications have yet to be realized.

Although it is impossible to predict the specific kinds of benefits that might accrue to the public, one need only look at a few examples of major problems to recognize that the technology is now available for new kinds of solutions. Some of FDA's research, for instance, has proceeded with the development of gene probes for the purpose of identifying pathogens at very low levels in food products. Other technologies can also be brought to bear on this problem that may be able to identify not only pathogens, but contaminants of many kinds including toxic chemicals. Some of these technologies could be packaged and marketed by private industry to the manufacturers, to importers, and to distributors of the food supply, who would then have the full capability of finding contaminated products before they get to the marketplace. In addition, state and local governments as well as the FDA could use some of these tools to screen products already in the marketplace and to protect against contaminated imported food. It is clearly in the best interest of the consumer that these products be developed as quickly as possible. Some of the new biotechnology firms, as well as the existing industry, have the capability to do this. But that capability could be expedited through cooperative R&D agreements with FDA laboratories.

There are other potential opportunities for similar kinds of advancements. Not only is there the potential for commercialization of technology from FDA laboratories, there is a significant opportunity for more resources around the country to be focused on the scientific problems faced by the Agency. Opportunities for increased academic collaboration, for instance, will strengthen the base of the scientific information upon which FDA must make decisions. To address these issues, FDA will undertake, at a minimum, seven major initiatives. FDA will:

1. Implement the provisions of the Federal Technology Transfer Act of 1986 to the fullest extent possible;
2. Develop an FDA committee for the purposes of developing an implementation plan and the mechanism for understanding the issues involved;
3. Develop a policy review board to consider the propriety of individual actions and to review ethical considerations associated with them;
4. Develop an outreach program to interact with academia, private industries, and others who seek more information about FDA technologies;
5. Develop a critical problem list of those problems of significance in public health terms where technological innovation would significantly enhance consumer protection;
6. Identify methods of encouraging employees to commercialize inventions through a quick and easy process of approval, patent application, and licensure; and
7. Review opportunities for provisions of the Technology Transfer Act to improve both the thoroughness of data utilized and the timeliness of product review procedures.

In summary, the initiatives undertaken by FDA will *significantly improve its capacity as an important facilitator of technology transfer; addressing in a more timely, effective, and efficient fashion the technology transfer needs of the American public.*

APPENDIX A

FDA POLICY BOARD

Frank E. Young, M.D., Ph.D.
Commissioner of Food and Drugs

John A. Norris, J.D., M.B.A.
Deputy Commissioner of Food and Drugs

Gerald L. Barkdoll, D.P.A.
Associate Commissioner for Planning and Evaluation

Hugh C. Cannon
Associate Commissioner for Legislative Affairs

Mary Ann Danello, Ph.D.
Special Assistant for Science

R. Alexander Grant
Associate Commissioner for Consumer Affairs

Gerald B. Guest, D.V.M.
Director, Center for Veterinary Medicine

Marlene E. Haffner, M.D.
Acting Director, Office of Orphan Products Development

Ronald W. Hart, Ph.D.
Director, National Center for Toxicological Research

Sharon S. Holston
Acting Associate Commissioner for Management and Operations

Joseph A. Levitt, Esquire
Executive Assistant to the Commissioner

Mary Frances Lowe
Senior Assistant to the Commissioner for Program Policy

Jack W. Martin
Associate Commissioner for Public Affairs

Sanford A. Miller, Ph.D.
Director, Center for Food Safety and Applied Nutrition

Stuart L. Nightingale, M.D.
Associate Commissioner for Health Affairs

Paul D. Parkman, M.D.
Acting Director, Center for Drugs and Biologics

Thomas Scarlett, Esquire
Chief Counsel

John Taylor
Associate Commissioner for Regulatory Affairs

Percy Thomas, Ph.D.
Director, Office of Equal Employment and Civil Rights

John C. Villforth
Director, Center for Devices and Radiological Health

APPENDIX B

ACTION PLAN PHASE I EXECUTIVE SUMMARY

This Action Plan is designed to fulfil the Secretary's charge of preparing FDA for the challenges of today and of the 21st century. The plan designates FDA's highest priorities and charts a broad course for the Agency's policy and management directions in the years ahead. The plan was based on extensive meetings that the Commissioner held with persons from both inside and outside the Agency. The Action Plan may be summarized as follows:

1. **New Drug Review Process.** FDA will make significant improvements in its new drug review process for human drugs, with the aim of further accelerating the review process while improving quality. FDA will begin by efficiently, effectively, and sensitively taking the following actions: implementing the new IND/NDA regulations; developing new models for conducting NDA reviews; reducing the backlog of supplemental NDAs; enhancing the use of automated data systems; and fully implementing the new program for post-1962 ANDAs.
2. **Medical Device Program.** FDA will prepare specific recommendations to respond efficiently, effectively, and sensitively to the legitimate criticisms that have been made about the Agency's implementation of the Medical Device Amendments of 1976. Special attention will be directed to those issues relating to bringing new products to market; premarket notifications [510(k)s]; premarket approval (PMA) applications; preamendments PMAs; and investigational device exemptions (IDEs).
3. **Postmarketing Surveillance.** FDA will strengthen significantly its postmarketing surveillance activities to enhance consumer protection against new and unforeseen risks with marketed products. Actions will include; working with health professionals to promote prompt, more complete reporting of adverse drug reactions; successfully implementing the new drug and device regulations; and upgrading current programs, where necessary, to ensure adequate surveillance of all human drugs, biologics, new animal drugs, and food products.
4. **Risk Assessment.** FDA will develop a comprehensive program to evaluate and test, where practicable, the assumptions used in risk assessment. The Agency will focus primarily on assessing the risk to humans of compounds contained in the food supply that have been found to cause cancer in laboratory animals. This program will be coordinated with other Federal agencies having an interest in risk assessment.
5. **Risk Management.** FDA will make significant improvements in its risk management process, with particular emphasis on early analysis of options, optimal utilization of FDA's full range of regulatory tools (i.e. education, enforcement, regulation, and voluntary compliance), organization of FDA's field operations, and coordination with other Federal, state and local agencies.
6. **Food Safety.** FDA will continue to work toward the resolution of food safety issues by administrative or legislative means, as appropriate.
7. **Nutrition.** FDA will significantly broaden its nutrition program to advance the science of nutrition, increase consumer awareness about nutrition, and provide continued assurance of the nutritional quality of the Nation's food supply. FDA will coordinate these activities with the United States Department of Agriculture (USDA) and the National Institutes of Health (NIH).
8. **New Technologies.** FDA will undertake to develop specialized internal capabilities in those new technologies most likely to dominate new medical developments and changes in the food supply, with particular emphasis on biotechnology and microelectronics.
9. **Health Fraud.** FDA will implement a significantly broadened initiative aimed at reducing health fraud, including both increased emphasis on enforcement activities and increased efforts at achieving consumer and health professional awareness. Particular attention will be given to focused efforts on health fraud creating health hazards and life threatening dangers.
10. **Internal Management.** FDA will make significant improvements in its own internal management, particularly in the areas of career advancement, information systems, laboratory research programs, resource allocation and science base. Particular attention will be given to the Commissioner's Advancement Program designed to meet the personnel needs of the FDA.

The Agency has profited for the analysis that has led the development of this Action Plan and looks forward to implementing these programs under its implementation plan. FDA is confident that these steps will not only prepared the Agency for the 21st Century, but will also strengthen the Agency's current programs. The Action Plan is described in greater detail in the Body of this report.

TOTAL NUMBER OF GOALS, OBJECTIVES, AND MILESTONES

	GOAL	OBJECTIVES	NUMBER OF MILESTONES	ACTUAL STARTS		ACTUAL COMPLETIONS	
				NUMBER	PERCENT	NUMBER	PERCENT
	1	7	31	31	100	29	94
	2	4	15	14	93	12	80
	3	8	48	43	90	38	79
	4	4	16	16	100	12	75
	5	4	11	11	100	11	100
	6	2	6	6	100	6	100
	7	6	29	27	93	23	79
	8	3	30	30	100	25	83
	9	3	27	27	100	25	93
	10	8	45	45	100	45	100
TOTALS	10	49	258	250	97	226	88

APRES STATUS AS OF APRIL 30, 1987

OBJECTIVES AND MILESTONES BY ORGANIZATIONS

ORGANIZATION	OBJECTIVES	NUMBER OF MILESTONES	ACTUAL STARTS		ACTUAL COMPLETIONS	
			NUMBER	PERCENT	NUMBER	PERCENT
CDB	11	58	53	91	47	81
OHA	1	5	5	100	5	100
CDRH	6	30	29	97	23	77
CVM	1	2	2	100	2	100
CFSAN	8	45	43	96	38	84
NCTR	4	16	16	100	12	75
ORA	9	38	38	100	37	97
SAB	3	6	6	100	6	100
OCA	2	34	34	100	32	94
OMO	4	24	24	100	24	100
TOTALS	49	258	250	97	226	88

APRES STATUS AS OF APRIL 30, 1987

Commissioner YOUNG. The most important thing that I will try to accomplish today is to cut through a large amount of the scientific jargon. The way I tackled this after you and I first talked and you suggested that I look very carefully into this was to function as a physician and try to make sense of what these different levels of intake really meant and how they were established.

The jargon is first to look for a no-effect level. That is from a lifetime animal study. In this particular case, rodents were fed up to 15 percent of their total diet as aspartame. This is an extraordinarily large amount. We usually go no more than about 5 percent of the diet, and we see 15 percent in this case.

The no-effect level was established here, because at this level, it was felt that there was some loss of weight, some pancreatic problems. But I must hasten to add that when you are dealing with 15 percent levels, it is hard to know whether we really have a no-effect. We took that arbitrarily.

In order to deal with the no-effect level and to translate that into what is called an acceptable daily intake (ADI), one usually, if you have no human data and are only basing it on animal data, will drop down a factor of 100 from this no-effect level.

I must hasten to add that the acceptable daily intake relates to a lifetime exposure of the animal. It is not an acceptable daily intake for a day; it is an acceptable daily intake over the entire life of the individual. And in this case, you see that this level dropped originally from the no-effect level of 2,000 to 20 milligrams per kilogram. As we had more information, we compared this number to others around the world, and with further human information we moved to a level of 50 milligrams per kilogram.

The actual intake, from information that I have presented to you in my testimony, is at the level of 2 to 4 milligrams per kilogram per day. So that when we are looking at this analysis, we are really 1,000-fold below the range that we had in the no-effect level.

You will be dazzled and at times confused by a wide variety of scientific presentations. Fortunately, I was provided with some of the information beforehand from the testimonies, and you will see focused the effect on phenylalanine in relation to brain metabolism; the focus in heterozygotes, those people who carry the traits for phenylketonuria; and you will also see some testimony that will deal with the amount of serotonin and dopamine that is synthesized.

The real issue that we face today is determining what the sequence of reality is as we look at these hypotheses. Science is a moving target. I had the privilege of working in a research laboratory for over a quarter of a century, and I know today's hypothesis will be frequently replaced by tomorrow's paradigm. This is not the Wild West when it comes to FDA. We have to go on facts. We have to deal with the best type of facts and try to use that rather than link particular studies on particular points in time.

And I look forward to seeing the transcript that will be provided as well on this. I have some interesting information that I will provide on our study, because following your and my interactions on this, I committed to do some further studies to be sure that the information was not based on just corporate-sponsored studies, as good or as poor as they might be perceived to be, but to try to do some government studies as well. And we have conducted three studies, or are in the process of dealing with three studies, with an aggregate cost over a total of $800,000. When you look at the meager resources that we have for research of about $3 million per year, $800,000 over a couple of years is between 15 and 20 percent of the resources that we have available. So we have not shied from what we feel our responsibility is in focusing on that.

[Information supplied for the record follows:]

SUBMISSION FOR THE RECORD

NOTE.—Submission: [The "information that I will provide on our study" referred to by the Commissioner is the same information mentioned again on page 13, lines 3-4—see next item. We are providing information on three studies under submission for page 13. The "transcript that will be provided", mentioned in lines 23-24 is, in our opinion, the Commissioner referring to a complete transcript of the aspartame hearing.]

Commissioner YOUNG. The particular studies that we have dealt with are as follows. We have looked at, with Battelle, a three-year contract for $678,772 that was awarded in September of 1986. This project is designed to focus on "the dietary amino acids and brain function." These studies will focus on the effect of altered amino acid balance on neurochemistry.

And as I want to point out again, this was in response to your concern, as we discussed, to be sure that we had the Federal Government sponsor studies as well.

The second is a two-year interagency agreement for $92,440 that was initiated on February 19th, 1987, at the National Institute for Environmental Health Studies in Research Triangle Park. This project is entitled, "Dietary Peptides and Behavior." Studies that affect the changes in amino acid balance on seizure threshold will be studied here. And we have submitted for the record, appended to my testimony, the abstracts of these studies.

[Information supplied for the record follows:]

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: Synopses and status report for three FDA contracted studies on aspartame.

A. Contract No. 223-87-2095 with Battelle Memorial Institute to study dietary amino acids and brain function.

B. Interagency Agreement No. 224-87-2436 with National Institute of Environmental Health Sciences to evaluate whether specific alterations of dietary amino acids which serve as neurotransmitter precursors can alter certain brain parameters in animal test systems.

(Note: Latest research findings will be obtained from the principal investigator and forwarded under separate cover).

C. Interagency Agreement No. 224-88-2435 with the Federal Aviation Administration in the area of cognitive behavioral effects from use of substances ingested as food additives.

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0. FDA CONTRACTED STUDIES: SYNOPSIS OF THREE CONTRACTS

BATTELLE

1. ~~BATTLE~~--A three-year contract (#223-86-2095) for $678,772 was awarded September 30, 1986, to Battelle Memorial Institute, Columbus Division. This project, entitled "Dietary Amino Acids and Brain Function" studies consequences of altered amino acid balance on neurochemistry, particularly neurotransmitters in animals.

2. NIEHS--A two-year Interagency Agreement (#224-87-2436) for $92,440 was initiated February 19, 1987, with the National Institute for Environmental Health Sciences, Research Triangle Park. This project, entitled "Dietary Peptides and Behavior" studies effects of changes in amino acid balance on seizure threshold or other neurobehavioral function in animals.

3. FAA--A two-year Interagency Agreement (#224-88-2435) for $99,390 was initiated October 1987 with the Federal Aviation Administration, Oklahoma City. This project, entitled "Effects of Aspartame and Related Compounds on Human Performance" studies effects of ingestion of aspartame by volunteer humans on performance in tests of cognitive function.

STATUS OF EXTRAMURAL PROJECTS RE: ASPARTAME

The FDA is actively engaged in developing appropriate test models with which to evaluate potential affects of food additives on the nervous system. As part of this effort the FDA is currently sponsoring three extramural projects investigating central nervous system neurochemical and behavioral function:

1. A three year contract (#223-86-2095) for $678,772 was awarded September 30, 1986, to Battelle Memorial Institute, Columbus Division. This project, entitled "Dietary Amino Acids and Brain Function" studies consequences of altered amino acid balance on neurochemistry, particularly neurotransmitters in animals.
2. A two year Interagency Agreement (#224-87-2436) for $92,440 was initiated February 19, 1987, with the National Institute for Environmental Health Sciences, Research Triangle Park. This project, entitled "Dietary Peptides and Behavior" studies effects of changes in amino acid balance on seizure threshold or other neurobehavioral function in animals.
3. A two year Interagency Agreement (#224-88-2435) for $99,390 was initiated October, 1987 with the Federal Aviation Administration, Oklahoma City. This project, entitled "Effects of Aspartame and Related Compounds on Human Performance" studies effects of ingestion of aspartame by volunteer humans on performance in tests of cognitive function.

Status of Battelle contract (#223-86-2095)

The overall objectives include the following:

1. to develop an experimental rodent model which will enable the detection and interpretation of diet-induced changes in brain function,

2. to determine the extent to which the ingestion of aspartame and other related compounds, which might alter amino acid balance, may affect brain neurotransmitter functions, and

3. to determine whether the treatment-related neurochemical changes, if any, are dependent upon such experimental conditions as route or duration of administration, nutritional status, sex or circadian cycle.

The contractor has developed and submitted a detailed scientific plan describing the experiments to be conducted. The final draft of this plan is being reviewed for approval by the Project Advisory Group. The contractor has proceeded with development and validation of the neurochemical methodology to be used and standard operating procedures in compliance with Good Laboratory Practices.

Status of the NIEHS Interagency Agreement (#224-87-2436)

Under this Interagency Agreement, the NIEHS is to evaluate the changes in brain excitability and behavior of adult and developing animals exposed acutely or repeatedly to compounds which may alter the endogenous levels of neurotransmitter precursors. Endpoints are to include measures of seizure proneness, particularly with regard to electrically kindled seizures, sensorimotor reactivity, and cognitive function. Comparisons of intraperitoneal vs. intragastric dosing are to be made. Depending on the outcome of these initial experiments, further studies will be conducted using specific amino acids e.g. phenylalanine and aspartic acid.

A series of experiments have already been completed. Acute intragastric administration of aspartame in doses up to 1,000 mg/kg had no significant effect on routine measures of sensorimotor function, including acoustic startle response, prepulse inhibition of startle, or spontaneous motor activity. These tests have been used frequently to assess chemical-induced alterations in central nervous system arousal and behavioral reactivity to environmental stimulation. Similar doses were found to have no significant effect in two different tests of learning and memory. Aspartame at total doses of up to 2,000 mg/kg was also found to have no significant effect on threshold of electrically kindled seizures.

Intraperitoneal administration of aspartame at doses up to 500 mg/kg had no effect on spontaneous motor activity.

Repeated daily dosing (14 days) with aspartame at doses up to 1,000 mg/kg/day revealed no effects on either spontaneous motor activity or learning behavior.

Status of the Interagency Agreement with the FAA (#224-87-2435)

This is a new Interagency Agreement (IAG) with the Federal Aviation Administration (FAA). Responding to an American Medical Association recommendation, the FAA currently has contracts with three research centers for testing cognitive performance in pilots. The test sites are the Institute of Aviation Medicine at the University of Illinois, Champaign, IL, Wright Civil Aeronautic Medical Research Center, Dayton, OH, and the Department of Neurology, Georgetown University, Washington, DC. Each center has a core of cognitive tests (e.g. logical reasoning, visual tracking, mental arithmetic) and additional tests emphasizing each centers' particular strengths (e.g. EEG recordings, flight performance tests using simulators). Tests are being validated against responses of individuals with diagnosed organic brain dysfunction.

This IAG allows additional tests for effects of acute ingestion of aspartame (up to the allowable daily intake, 50 mg/kg) in those same subjects. The high precision in performance of these subjects maximizes the sensitivity of the tests. The design uses each individual as their own control, and includes testing of placebo, phenylalanine, or other physiological agents (e.g. ethanol, caffeine) which have previously been shown to affect performance in these tests (positive controls).

Depending on initial results, subsequent tests will investigate dose-response relationships, chronic aspartame ingestion, co-ingestion of aspartame with other dietary components (or amino acids), and/or tests in PKU heterozygotes and the general population.

"A"

OMB No. 0990-0109
OMB No. 0990-0115

AWARD/CONTRACT	1. THIS CONTRACT IS A RATED ORDER UNDER DPAS (15 CFR 350) ▶	RATING	PAGE OF PAGES
2. CONTRACT (Proc. Inst. Ident.) NO. 223-86-2095	3. EFFECTIVE DATE 9/30/86	4. REQUISITION/PURCHASE REQUEST/PROJECT NO. 315358	
5. ISSUED BY CODE HFA-530 DHHS/PHS/FOOD AND DRUG ADMINISTRATION Food Safety Contracts Branch 200 C Street, SW, Room 2831 Washington, DC 20204	6. ADMINISTERED BY (If other than Item 5) CODE Period of Performance: September 30, 1986 - September 29, 1989		
7. NAME AND ADDRESS OF CONTRACTOR (No., street, city, county, State and ZIP Code) Battelle Memorial Institute Columbus Division 505 King Avenue Columbus, Onio 43201-2693	8. DELIVERY ☐ FOB ORIGIN ☐ OTHER (See below) 9. DISCOUNT FOR PROMPT PAYMENT		
CODE FACILITY CODE	10. SUBMIT INVOICES (4 copies unless other wise specified) TO THE ADDRESS SHOWN IN ▶	ITEM	
11. SHIP TO/MARK FOR CODE	12. PAYMENT WILL BE MADE BY CODE HFA-530 Food and Drug Administration Food Safety Contracts Branch, Room 2831 200 C St., SW, Washington, DC 20204		
13. AUTHORITY FOR USING OTHER THAN FULL AND OPEN COMPETITION: ☐ 10 U.S.C. 2304(c)( ) ☐ 41 U.S.C. 253(c)( )	14. ACCOUNTING AND APPROPRIATION DATA 25.31 7560600 2234W/10 6-6991295-F-095 EIN: 31-4379427		

15A. ITEM NO.	15B. SUPPLIES/SERVICES	15C. QUANTITY	15D. UNIT	15E. UNIT PRICE	15F. AMOUNT
	Dietary Amino Acids and Brain Function	(Cost Plus	Fixed	Fee)	$678,772.00
				15G. TOTAL AMOUNT OF CONTRACT ▶	$ 678,772.00

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(✓)	SEC.	DESCRIPTION	PAGE(S)	(✓)	SEC.	DESCRIPTION	PAGE(S)
		PART I – THE SCHEDULE				PART II – CONTRACT CLAUSES	
X	A	SOLICITATION/CONTRACT FORM	1	X	I	CONTRACT CLAUSES	21
X	B	SUPPLIES OR SERVICES AND PRICES/COSTS	2			PART III – LIST OF DOCUMENTS, EXHIBITS AND OTHER ATTACH.	
X	C	DESCRIPTION/SPECS./WORK STATEMENT	3		J	LIST OF ATTACHMENTS	24
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X	F	DELIVERIES OR PERFORMANCE	12				
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X	H	SPECIAL CONTRACT REQUIREMENTS	18		M	EVALUATION FACTORS FOR AWARD	

CONTRACTING OFFICER WILL COMPLETE ITEM 17 OR 18 AS APPLICABLE

17. ☒ CONTRACTOR'S NEGOTIATED AGREEMENT (Contractor is required to sign this document and return 3 copies to issuing office.) Contractor agrees to furnish and deliver all items or perform all the services set forth or otherwise identified above and on any continuation sheets for the consideration stated herein. The rights and obligations of the parties to this contract shall be subject to and governed by the following documents: (a) this award/contract, (b) the solicitation, if any, and (c) such provisions, representations, certifications, and specifications, as are attached or incorporated by reference herein. (Attachments are listed herein.)	18. ☐ AWARD (Contractor is not required to sign this document.) Your offer on Solicitation Number ______ including the additions or changes made by you which additions or changes are set forth in full above, is hereby accepted as to the items listed above and on any continuation sheets. This award consummates the contract which consists of the following documents: (a) the Government's solicitation and your offer, and (b) this award/contract. No further contractual document is necessary.
19A. NAME AND TITLE OF SIGNER (Type or print) W. MICHAEL [illegible] CONTRACTING OFFICER	20A. NAME OF CONTRACTING OFFICER Thomas H. Vargo
19B. NAME OF CONTRACTOR BY ______ (Signature of person authorized to sign) — 19C. DATE SIGNED SEP 24 1986	20B. UNITED STATES OF AMERICA BY ______ (Signature of Contracting Officer) — 20C. DATE SIGNED 9/25/86

NSN 7540-01-152-8069
PREVIOUS EDITION UNUSABLE

26-106

STANDARD FORM 26 (REV. 4-85)
Prescribed by GSA
FAR (48 CFR) 53.214(a)

U.S. GOVERNMENT PRINTING OFFICE : 1985 O-[illegible]

SECTION B - SUPPLIES OR SERVICES AND COSTS

B.1 Compensation

B.1.1 Estimated and Allowable Cost

B.1.1.1 It is estimated that the total cost to the Government for full performance of this contract will be $678,772.00 of which the sum of $646,121.00 represents the estimated allowable reimbursable cost in accordance with FAR 52.216-7 (Allowable Cost and Payment - April 1984) and $32,651.00 represents the fixed fee.

B.1.1.2 This contract is fully funded for the three (3) year period of performance. The estimated total cost and performance period for each phase is as follows:

Phase I - Scientific Plan (4 mos.)	$ 12,600.00
Phase II - Methodology (5 mos.)	90,213.00
Phase III - Good Laboratory Practices (3 mos.)	23,111.00
Phase IV - Experimentation (24 mos.)	552,848.00
TOTAL	$678,772.00

B.1.1.3 Total expenditures for domestic travel as described below (transportation, lodging, subsistence, and incidental expenses) incurred in direct performance of this contract shall not exceed $2,265.00 without the prior written approval of the Contracting Officer.

1. Travel by motor vehicle including rented automobile shall be reimbursed on a reasonable actual expense basis, or at the contractor's option, on a mileage basis at a rate of 20.5 cents per mile, plus any toll or ferry charges.

2. Reasonable actual costs of lodging and subsistence, or per diem in lieu of actual costs, shall be allowable to the extent that such actual costs or per diem amounts do not exceed $112.00 per day.

3. "Air coach" or "Air tourist" accommodations on prop or jet constitutes the normal class of air travel which shall be utilized. First-class accommodations may be used if (1) less than first-class is not available providing reservation is requested within 24 hours after the traveler has knowledge of the trip; (2) less than first-class required circuitous routing; (3) less than first-class requires travel to begin or end at unreasonable hours (i.e., if scheduled flight time is before 8:00 a.m. and scheduled arrival is after 9:00 p.m.); (4) less than first-class will result in additional direct costs which will offset the transportation savings; or (5) less than first-class will not make connections with other flights or means of transportation for continuation of the journey.

4. The cost of rail travel by most direct route, first-class with lower berth or nearest equivalent shall be utilized.

B.1.1.4 Pending the establishment of final overhead rates as provided for in the clause entitled, "Allowable Cost and Payment" (April 1984) in Part II, Section I of the contract, the Contractor shall be reimbursed for indirect costs on the basis of the negotiated provisional rates set forth below. The rates shall remain in effect until the contract is amended to incorporate either (a) final overhead rates for a specific period or periods, or (b) revised negotiated provisional overhead rates as provided for in paragraph (d) of the clause.

1. Overhead = 34% of Direct Labor
2. General Administrative Expense = 82% of Direct Labor

B.1.1.5 Notwithstanding the clause entitled "Subcontracts Under Cost-Reimbursement and Letter Contracts" (April 1984) in Part II, Section I of this contract, any item of equipment having a unit acquisition cost in excess of $1,000.00 for which the contractor is to be reimbursed as a direct item of cost, shall not be acquired by the contractor without the specific advance written approval of the Contracting Officer.

B.1.2 Provisions Applicable to Direct Costs

Notwithstanding the clauses entitled "Allowable Cost and Payment and Fixed Fee" (April 1984) and "Subcontracts Under Cost-Reimbursement and Letter Contracts" (April 1984) in Part II, Section I of the contract, unless otherwise expressly provided elsewhere in this contract or in any amendment thereto, the costs of the following items or activities shall be unallowable as direct costs:

1. Acquisition, by purchase or lease, or any interest in real property;
2. Special rearrangement or alteration of facilities;
3. Purchase or lease of any item of general purpose, office furniture, or office equipment;
4. Travel to Foreign Countries. See the clause entitled "Foreign Travel" (April 1984) in Part II, Section I of the contract.

SECTION C - DESCRIPTION SPECIFICATION/WORK

C.1. Scope of Work

C.1.1 FDA realizes that there are numerous approaches to developing an animal model system required under this contract. For ease of contract administration and to allow maximum flexibility to the contractor, the contract shall be divided into a series of phases. Each phase shall be approximately in six (6) months in duration. Alternative research approaches may be proposed to accomplish the objectives of this contract. Any variation in the approved Scientific Plan shall have prior Government review and approval.

C.1.2 Objectives

The overall objectives of this contract are the following:

1. to develop an experimental animal (rodent) model which will enable the detection and interpretation of biologically significant changes in brain function, particularly as they relate to the potential nutrition-brain interrelationships and possible biochemical mechanisms involved,

2. to determine the extent to which the ingestion of aspartame and other related compounds which might result in changes of amino acid balance, may affect the functional state of synaptic/receptor activity of selected neurotransmitters, including the serotonergic, noradrenergic and dopaminergic systems, and

3. to determine whether the characteristics of any treatment-related neurochemical changes, vary with the experimental conditions, such as different routes of administration, dietary status of the animals, duration of exposure to the experimental treatments, and the circadian cycle.

C.1.3 Literature Citations and Other References

See Section J.

C.1.4 Background

C.1.4.1 The FDA is one of the primary agencies of the US Government with responsibility for the safety of the food supply. Chemicals present in food as food additives or contaminants are extensively tested and evaluated for potential toxic effects on the human population (Hattan et al., 1983). Currently there is a need to develop an animal model to identify the appropriate questions that need to be addressed in evaluating the safety of food chemicals for neurochemical and neurobehavioral effects. These are relatively new aspects of food safety which have arisen as a result of recent advances in the field of toxicology and the development of new products by the food industry for use in the general population. An example of this type of food product is aspartame, a dipeptide sweetener consisting of the amino acids phenylalanine and aspartic acid. Other peptides are being developed as sweeteners and as substitutes for salt, and specific amino acids, such as tryptophan, are being tested for their capacity to induce specific neurobehavioral changes, such as sleep. Whether consumed as peptides or amino acids, these compounds are metabolically indistinguishable from other dietary amino acids, yet any change in the balance of amino acids, especially when large doses are consumed, has the potential to affect neurochemical processes.

C.1.4.2 Several of these amino acids serve as dietary precursors for neurotransmitter substances in the central nervous system. Hence, a fundamental question has arisen as to whether dietary exposure to such amino acids can modulate central neurotransmitter systems and, if so, could this result in significant changes in brain function and behavior. Under the normal toxicological testing and review process, frank toxicity such as neurological dysfunction and neuropathological changes would be readily detected, whereas more subtle changes in brain function and behavior might not be detected. Resolving the persistent questions about the potential effects of aspartame and other dietary components on the central nervous system is one aspect of food safety which the FDA must address as the responsible regulatory agency. The question is whether and under what conditions, can dietary substances cause changes in the levels and turnover rates of neurotransmitters, and whether these neurotransmitter changes produce abnormal physiological and/or neurobehavioral changes. At this time, there is insufficient knowledge relating diet, neurotransmitters, and brain function, but it is a rapidly developing area in the neurosciences (Leprohon-Greenwood and Anderson, 1986). The relatively inconclusive state of knowledge in this field of science explains in part the difficulties of formulating a regulatory strategy and the need for this contract to develop animal test systems to help answer these questions.

C.1.4.3 Other questions to be addressed include: (1) does exposure to aspartame result in consistent and reproducible changes in brain neurochemistry under different experimental conditions including such factors as route of adminstration, fasting, the use of single or divided doses, dosing at different times of the circadian cycle, and acute versus chronic exposure; and (2) are these effects unique to aspartame or are they common to other dietary or treatment conditions which modify amino acid availability.

C.1.5 Analysis of current research reports on the neurochemical and neurobehavioral effects of aspartame

C.1.5.1 The dietary amino acids phenylalanine, tryptophan, threonine, glutamine and glycine serve directly or indirectly as precursors for brain and peripheral neurotransmitters. A major area of interest therefore has centered on the question of whether loading with high levels of any of these dietary precursors has the potential to affect brain amino acid and neurotransmitter levels and behavior itself. In recent years this interest has focused on the artificial sweetener aspartame as a dietary source of phenylalanine and aspartic acid. A large body of data from studies submitted to the FDA (Food Additive Master Files 134 and 290; Stegink and Filer, 1984) exists to support the conclusion that the no-observed-effect-level (NOEL) for aspartame in laboratory animals based on results from traditional toxicological testing is at least 2000 mg/kg. The data obtained from neurobehavioral and developmental studies that have been performed with aspartame are basically in agreement with this NOEL (Brunner et al., 1979; Stegink and Filer, 1984).

C.1.5.2 A series of screening studies was conducted by Potts et al. (1980) to test for neuropharmacological properties of aspartame. Mice or rats were given aspartame up to 1000 mg/kg body weight as an intragastric bolus dose. Testing involved such measures as motor coordination, hexobarbital potentiation, analgesic activity, anticonvulsant and antidepressant activity, and learning behavior. At these dosage levels, the authors reported no biologically significant effects. In addition, these authors also conducted more extensive behavioral studies, involving measures of general motor activity, and conditioned and unconditioned avoidance responses following administration of phenylalanine at dietary levels of 2.5% and 5.0% (equivalent to daily doses of 3,050 to 6,100 mg/kg), and aspartame at dietary levels of 4.5% and 9.0% (equivalent to daily doses of 5,500 to 11,000 mg/kg) (Potts et al., 1980). Only the highest levels of phenylalanine (6,100 mg/kg) and aspartame (11,000 mg/kg) elicited consistently significant effects in these tests.

C.1.5.3 G. D. Searle has also sponsored a behavioral study in stump-tailed macaques which was presented at the aspartame Public Board of Inquiry in 1980 (Food Additive Master Files 134 and 290; Stegink and Filer, 1980). Neonatal monkeys were administered 0,1, 2 or 3 g aspartame/kg body weight in their feed for nine months (developmentally equivalent to 3 years in the human infant). The monkeys were tested for electroencephalographic (EEG) changes which are indicative of seizure susceptibility but no such changes were observed. After aspartame was withdrawn from these monkeys, both control and aspartame-treated animals were subjected to a broad range of neurobehavioral testing at the Wisconsin Primate Center of the University of Wisconsin. In none of the tests of sensory, motor, integrative or cognitive functions was there a difference between the control and aspartame-treated groups. It was concluded that exposure to these very high levels of aspartame caused no neurological abnormalities.

C.1.5.4 Recently, a study has been performed to assess whether the behavior of hyperactive children is adversely affected by sucrose (Wolraich et al., 1985). In this study, 57.3 g (1.75 g/kg) of sucrose or 197 mg (6 mg/kg) of aspartame were given as a single challenge drink to boys who met the diagnostic criteria of hyperactivity. The measures of behavior were playroom observation, continuous performance tests, paired associate learning test, nonsense word spelling task, and "draw a line slow" test. Aspartame was used as a placebo in this study, and no difference was found in the behavioral measures examined in the hyperactive boys between baseline (control) responses and the responses after administration of aspartame or sucrose.

C.1.5.5 Inspite of much evidence to indicate that aspartame does not cause behavioral changes in rats, mice, and primates under a variety of laboratory conditions, several investigators in the scientific community have continued to argue that high doses of the sweetener may affect brain neurotransmitter levels and behavior in certain susceptible groups of the human population (Coulombe and Sharma, 1986; Wurtman, 1983). Aspartame provides phenylalanine and, indirectly, tyrosine as precursors of the neurotransmitters, dopamine and norepinephrine. In addition, by modulating plasma ratios of amino acids, there is the potential for modifying brain tryptophan levels and, subsequently, the neurotransmitter serotonin. Fernstrom et al., (1983) showed that, although high doses of aspartame (200 mg/kg body weight) given by gavage to rats increased plasma and brain phenylalanine and tyrosine levels, there were no significant changes in neurotransmitter levels measured in whole brain. In a similar study in rats, Yokogoshi et al. (1984) found that the rise in brain phenylalanine following high doses of aspartame (200 mg/kg) was markedly potentiated by glucose. In addition they reported that the changes in brain 5-hydroxyindoles normally caused by glucose were blocked by high doses of aspartame. These interactive effects were thought to be mediated by the plasma amino acid composition resulting from the presence of the amino acid components of aspartame and the glucose-induced release of insulin. Since aspartame flavored drinks might be consumed with carbohydrate snacks, it was claimed that the potential impact of aspartame in man was not fully evaluated. In later studies, Yokogoshi et al., (1986) measured regional brain neurotransmitter levels in the spontaneously hypertensive rat (SHR) and two nonhypertensive strains, the Wistar Kyoto (WKY) and Sprague Dawley rat. Following administration of aspartame or tyrosine (200 mg/kg), tyrosine levels in most brain regions were increased, while norepinephrine levels were increased or decreased depending on the specific brain area and the strain of rat. The norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG), was increased in discrete brain regions.

C.1.5.6 One of these authors (Wurtman 1983), has also claimed that aspartame completely blocks the changes in 5-hydroxyindoles caused by glucose, but, in later studies by Fernstrom et al (1986), the effect of aspartame on carbohydrate-induced tryptophan levels and hydroxylation rate was only observed at the very high dose of 530 mg/kg. Two recent papers by Torii et al. (1986a,b), failed to show any changes in whole brain monoamine levels, or any effect on consummatory behavior and general motor activity in rats following 250 mg/kg doses of aspartame.

C.1.5.7 Studies in mice recently reported by Coulombe and Sharma (1986) show that high doses of aspartame (up to 650 mg/kg body weight) administered by corn oil gavage increased levels of norepinephrine and dopamine in various brain regions, particularly the hypothalamus. This effect was observed at 3 hours but not at 6 and 24 hours. There were no changes in regional levels of serotonin or its metabolites at any of the time periods studied. Subchronic studies in mice were also performed on the effects of administration for 30 days with 0, 13, 133 and 650 mg/kg of aspartame. In these studies, the regional changes in catecholamines were not observed, but the levels of serotonin and some of its metabolites were decreased in several brain regions. The results suggest that during chronic exposure certain adaptive mechanisms compensate for exposure to high doses of the transmitter precursors of phenylalanine and tyrosine. No behavioral studies were conducted to determine whether the neurotransmitter changes were associated with any modification of brain function in mice.

C.1.5.8 This partial review of the literature on neurochemical and behavioral effects of aspartame indicates little consensus on the effects of this material in the systems studied by the numerous investigators. Furthermore, the effects that have been observed in any series of experiments appear to depend to a large extent on the conditions used in the experiment. Hence, although statistically significant changes in neurotransmitter levels and turnover rates in brain regions of rats and mice have been observed following very high doses of aspartame, it is not yet possible to know whether these changes are behaviorally or otherwise biologically significant, or whether such changes are typical of other types of dietary and circadian changes in the animal's environment. The fact that so little is known at this time about the inter-relationships between diet, neurochemistry and brain function underscores the need for the type of information sought in this contract. The availability of this information will facilitate our efforts to develop a basic model to address some of the questions being posed by the use of food additives such as aspartame which may not be answered by traditional toxicological testing.

C.1.5.9 To develop scientific data to meet these requirement, the project will fall into two general areas, neurochemistry and neurobehavior. The contract will emphasize the comparison of the neurochemical effects resulting from exposure to dietary components such as aspartame and other related substances, with changes that occur normally due to the diurnal variation associated with feeding and the light/dark cycle of the animal's environment. Although considerable research has been performed on the neurochemical effects of aspartame, the Agency believes that these studies have been deficient in relating the degree of change produced by aspartame to the normal variation that may occur in these parameters. Therefore, the information from this contract will provide important baseline (control) data that will be critical for determining the safety of these peptides and related compounds.

C.1.5.10 The biological significance of any change in neurochemical status must ultimately be based on a correlation with change(s) in the functional output of the brain. Consequently, it is essential that the animal model also include a qualitative and quantitative characterization of the behavioral and physiological changes associated with the dietary alteration. For this reason it is anticipated that the present contract will be extended to include a parallel study with tests to evaluate changes in brain function following ingestion of aspartame and other dietary treatments. The status of brain function will be based on an evaluation of a group of neurobehavioral endpoints representative of the range of functions controlled by the central nervous system, such as food intake, seizure threshold, sleep pattern, motor function, activity level, learning and memory, reaction time, pain threshold, blood pressure, and temperature regulation. It is hoped that the combination of the neurochemical and neurobehavioral studies will not only provide invaluable data for the Agency but will stimulate within the scientific community further basic research on the relationships between diet and brain function.

C.2 Coordination and Cooperation

C.2.1 The contractor shall coordinate this contract effort directly with the contracting officer or his/her authorized representative.

C.2.1.1 The Government will make all reasonable attempts to furnish information of on-going studies related to this contract effort to the contractor. However, the Government is in no way contractually obligated to furnish such information. The failure by the Government to furnish any information shall in no way relieve the contractor from complying with the requirements of this contract.

C.2.1.2 Independently and not as an agent of the Government, the contractor shall exert his/her best effort to furnish the necessary personnel, materials, services, facilities, and otherwise do all things necessary for or incidental to the performance of the work as described below.

C.3 General Requirements

C.3.1 All phases of the work shall be conducted according to the provisions of Good Laboratory Practices (GLP's). Unless otherwise stated in the experimental design, the following conditions shall be maintained as a standard throughout the study. Animals to be used for these experiments shall be adult rats, 60-90 days of age. Animals shall be housed individually in suspended stainless steel cages. The laboratory shall be maintained under standard conditions of controlled temperature and humidity and a regulated light/dark cycle. Water shall be continuously available throughout the study. The basal diet shall consist of the AIN-76 formulation.

C.3.1.1 A sufficient number of animals for each treatment and experimental condition shall be used to produce statistically valid data. The contractor shall specify the statistical techniques to be used for analysis of the data.

C.3.1.2 The problem to be addressed in the scope of work will focus on determining whether aspartame, related compounds, and specific dietary conditions such as high protein or high carbohydrate diets, induce any significant changes in specific neurotransmitter systems in the central nervous system. Within this context, two specific issues shall be addressed: (1) whether any treatment-related effects are specific to aspartame or might also be caused by other treatment conditions which can similarly result in changes in the amino acid balance, such as exposure to equimolar quantities of phenylalanine or aspartic acid; and (2) whether the occurence of any of the treatment-related effects might be dependent upon the experimental or environmental conditions under which the study is conducted, such as post-dose interval, route of administration, duration of exposure (acute versus chronic 30 day exposure), nutritional status of the animals (fasting versus ad libitum fed animals), diet composition (e.g. high protein or high carbohydrate), circadian period at which testing is conducted, or the sex of the animals.

C.3.1.3 The treatment conditions for this study shall include, but shall not necessarily be limited to aspartame, phenylalanine, and aspartic acid. A suitable series of doses should be selected for these studies.

C.3.1.4 The effects of the treatment parameters on brain neurotransmitter levels shall be based on brain regions, and not on total brain levels. The neurotransmitter substances to be measured include norepinephrine, dopamine and serotonin and their major metabolites that can readily be assayed by HPLC or other comparable techniques. Other transmitters might be included, such as acetylcholine and gamma aminobutyric acid (GABA), if considered to provide useful information and if the laboratory has the techniques established.

C.3.1.5 Since it has been well established in the peripheral nervous system that a major mechanism of regulation is mediated via changes in receptor function, the contractor is encouraged to investigate how the test substances might alter brain receptor levels for the respective neurotransmitters. This may be approached from traditional receptor measurements in membrane preparations, or using whole brain sections and measuring brain receptor levels by quantitative, computer-assisted, immunohistochemical or autoradiographic techniques.

C.4 Specific Requirements

C.4.1 Notification

The contractor shall not proceed with any expenditure for materials, labor, or any other work under any Phase described in this contract until receipt of a written notice to proceed is received from the Contracting Officer. If, in the judgment of the FDA, the objectives of the dietary amino acids and brain function contract are not achieved and are inconclusive, or there is a lack of funds, the contract may be terminated at the end of any Phase.

C.4.1.1 Phase I - Scientific Plan (approximately 4 months)

The contractor shall prepare a detailed Scientific Plan describing how he/she expects to address the questions cited under Section C of the contract, taking full consideration of the complexities of the issues and how the work will be accomplished. The Government will review, comment, approve, disapprove, or reject the Scientific Plan within 60 days after receipt.

C.4.1.2 Phase II - Methodology (approximately 5 months)

The contractor shall provide details of the methodology to be used in carrying out the approved Scientific Plan as required under Phase I. The contractor shall validate the methodology in terms of specificity and reproducibility, the applicability to regional brain analysis and the number of animals required for statistical significance. The Government will review, comment, approve, disapprove, or reject the Methodology within 60 days after receipt.

C.4.1.3 Phase III - Good Laboratory Practices (GLP's) (approximately 3 months)

The contractor shall design and develop Standard Operating Procedures according to the GLP's found in 21 CFR, Part 58. The Government will review, comment, approve disapprove, or reject the proposed procedures within 30 days after receipt.

C.4.1.4 Phase IV - Experimentation in (approximately 6 month segments until completion within - 24 months.

The contractor shall conduct experiments according to its approved Scientific Plan and SOP's. Test results and interpretation of those results shall be submitted to the Government for review in approximately 6 month segments. The Government will review the progress of the research and advise the contractor of the direction or redirection of the research for the next segment of research.

SECTION D - PACKAGING AND MARKING

D.1 Marking Instructions for Reports

The contractor shall mark each shipment with its organization name, contract number, item number, and quantity (indicate partial or final shipment). As appropriate, note on the face page of the report and when feasible on the binding (1) "one volume only" or (2) "volume 1 of 2, volume 2 of 2" etc.

D.2 Marking Instructions for End Items

1. The item(s) specified in Section C - Description/Specification/Work shall be packaged, packed, and shipped prepaid, to assure arrival at destination in an undamaged condition with proper handling.

2. The item(s) shall be marked with the contractor's name, contract number, item number(s) and quantity.

SECTION E - INSPECTION AND ACCEPTANCE

E.1 Inspection and Acceptance

Pursuant to the appropriate inspection clause in Part II, Section I of the contract, final inspection and acceptance of all items called for by the contract shall be made by the FDA Contracting Officer at the Food and Drug Administration, Food Safety Contracts Branch, 200 C Street, SW, Room 2831, Washington, DC 20204.

SECTION F - DELIVERIES OR PERFORMANCE

F.1 Reports/Deliverables

The contractor shall submit the following reports/deliverables:

F.1.1 Progress Report

The contractor shall submit eight (8) copies of a technical progress report to the Contracting Officer within 30 days after completion of work accomplished under a Phase and each work segment. These reports shall include:

1. summary of the progress during the period reported

2. technical and management problems of significance

3. problems anticipated in future reporting

4. summaries of important trips, conferences, meetings, briefings, during reporting period and those planned for following period

5. a statement that the contract can or cannot be completed on schedule and within total estimated cost and the reasons therefore.

6. include the title, type of report, and contract number

F.1.2 Phase/Segment Reports

The contractor shall submit eight (8) copies of a Phase/Segment Report to the Contracting Officer within thirty (30) days after completion of the work accomplished during a Phase or Segment. The report shall be in GLP format and include:

1. introduction
2. methods, results, discussion
3. summary tables with statistics
4. appendix including raw data

F.1.3 Draft Final Report

1. The contractor shall submit eight (8) copies of the draft final report to the Contracting Officer within 33 months after contract award. The draft final report shall include tables and graphs as necessary and in sufficient detail to explain (comprehensively), the results achieved under the contract. The format shall conform to GLP requirements.

2. The Government will review approve, disapprove a reject the draft final report within 30 days after receipt.

F.1.4 Final Report

The contractor shall submit (8) copies of the final report to the Contracting Officer with 60 days after receipt of the Government approval of the draft final report.

F.1.5 Financial Report

1. Financial reports on Form HHS-646, "Financial Report of Individual Project/Contract," shall be submitted by the contractor per the instructions which accompany the form, (in an original and two copies, not later than thirty (30) working days after the close of the reporting period). The line entries for subdivisions of work and elements of cost (expenditure categories) to be reported within the total contract shall be stated in subparagraph 4 below. Subsequent changes and/or additions in the line entries shall be made in writing.

2. The reports shall be submitted quarterly. The first financial report shall cover the period consisting of the (first full calendar month/first full three calendar months) following the date of the contract, in addition to any fractional part of the initial month.

3. If the final payment of this contract is to be made on the basis of a desk audit, the Contracting Officer may require the contractor to submit detailed support for costs contained in one or more interim financial reports.

4. Column A. of the Form 646 shall contain the following categories:

    Direct Material
    Direct Labor
    Overhead
    Travel
    Consultants
    Other Direct Costs
    General and Administrative

F.1.6 Subcontract Report

1. Summary subcontract report (SF 295)

    1. This report is required from Federal contractors and subcontractors, which are not small business concerns, and which hold one or more contracts over $500,000 ($1 million for construction) and have small and disadvantaged business concerns under a subcontracting plan. The report shall be submitted on Standard Form 295 (in accordance with the instructions which accompany the form) to:

        Department of Health and Human Services
        Director, Office of Small & Disadvantaged Business Utilization
        200 Independence Avenue, S.W.
        Washington, DC 20201

    2. The report shall be submitted quarterly and is due by the 25th of the month following the close of the reporting period as stated in the instructions which accompany the form. A copy of the report shall be submitted to the Contracting Officer.

2. Subcontracting report for individual contracts (SF 294)

    1. This report is required from Federal contractors and subcontractors which are required to establish plans for subcontracting with small and small disadvantaged business concerns. An original and one copy of the report shall be submitted to the Contracting Officer on Standard Form 294.

    2. The report shall be submitted semiannually on March 31 and September 30, as well as at contract completion, and is due by the 25th day of the month following the close of each reporting period as stated in the instructions which accompany the form.

F.2 Technical Briefings

1. Technical briefings consisting of oral/visual presentation shall be given by the contractor covering the progress period

and indicating initial findings, conclusions, and the direction to be pursued during the remainder of the contract. Additional technical briefings shall be given, highlighting the findings of the applicable phase/or segments and covering materials to be presented in the draft report. Briefings should be held at the FDA, 200 C Street, S.W., Washington, DC . Briefings may be held at alternative location(s) if approved by the Government.

2. The initial briefing shall be held no later than 60 calendar days after contract award and subsequent briefings shall be conducted within 30 days after submission of each Phase/Segment Report and prior to completion of the Government review. The contractor shall plan and schedule briefings with Government representatives.

3. The final briefing shall be held not later than 30 calendar days after the physical completion of research, i.e., 24 months after contract award. The briefing and recommendations shall be included in the final report.

F.3 Period of Performance

Performance of this contract shall begin on September 30, 1986 and shall not extend beyond September 29, 1989.

SECTION G - CONTRACT ADMINISTRATION DATA

G.1 Project Officer

The Project Officer responsible for the acceptance of work provided hereunder will be designated by separate correspondence.

G.2 Key Personnel

The individuals cited below are key personnel. (See Key Personnel Clause in Part II, Section I of the contract:

Name	Title
Dr. Gillian Haggerty	Principal Investigator

G.3 Invoice Submission

1. Pursuant to the provisions of the clause entitled, "Allowable Cost and Payment" (April 1984), in Part II, Section I of the contract, the Contractor shall submit vouchers or invoices in accordance with the following instructions:

2. An original and five (5) copies shall be submitted to the attention of the designated Contract Specialist at the following address:

   Department of Health and Human Services
   Food & Drug Administration
   Attention: Thomas H. Vargo
   Food Safety Contracts Branch, HFA-530
   200 C Street, SW, Room 2831
   Washington, DC 20204

3. The contractor shall furnish the following minimum information in support of costs submitted:

   1. Contractor's name and invoice date.
   2. Contract number or other authorization for delivery of property and/or services.
   3. Name where practicable, title, phone number, and complete mailing address of responsible official to whom payment is to be sent.
   4. Brief description of property and/or services actually delivered or rendered.
   5. Shipping and payment terms.
   6. Period of Performance for which costs are claimed.
   7. Labor hours/or percent of time as the case may be, segregated as to professional and nonprofessional.
   8. Overhead rate(s) and costs.
   9. Material costs, itemized in all cases.
   10. Equipment cost, itemized and identified including reference to approval in all cases and separated from material costs.
   11. General and Administrative rates and costs as applicable.
   12. Travel cost, itemized and identified including origin and destination.
   13. Any other supporting data that will clarify unusual expenditures.
   14. Fees if applicable.

4. The contractor shall include the costs for the current period and the cumulative costs for the total contract according to the categories shown above.

G.5 Title to Property

This contract is for scientific research and is with a nonprofit institution of higher education or with a nonprofit institution whose primary purpose is the conduct of scientific research. Therefore, under subparagraph (c)(2) of the clause entitled "Government Property (Cost-Reimbursement, Time-And-Material, or Labor-Hour Contracts)" (April 1984) in Part II, Section I of the contract, title to property having an acquisition cost of less than $1,000 shall vest in the contractor. Title to equipment having an acquisition cost of $1,000 or more, and purchased with research funds made available under contract, shall vest in the Government.

G.6 Progress Reviews

1. Periodic progress reviews shall be held at the contractor's facility by designated representatives of the Contracting Officer.

2. The initial progress review shall be held approximately 90 calendar days after contract award. Thereafter, progress reviews shall be held as deemed necessary by the contracting officer or his/her representative(s).

SECTION H - SPECIAL CONTRACT REQUIREMENTS

H.1 Warranty Against Dual Compensation

The contractor warrants that no part of the total contract amount provided herein shall be paid directly or indirectly to any officer or employee of the Department of Health and Human Services as wages, compensation, or gifts for acting as officer, employee, subcontractor, or consultant to the contractor in connection with any work contemplated or performed under or in connection with this contract.

H.2 Confidentiality of Information

1. Confidential information, as used in this clause means (1) information or data of a personal nature about an individual, or (2) proprietary information or data submitted by or pertaining to an institution or organization.

2. In addition to the types of confidential information described in (1) and (2) above, information which might require special consideration with regard to the timing of its disclosure may derive from studies or research, during which public disclosure of preliminary unvalidated findings could create erroneous conclusions which might threaten public health or safety if acted upon.

3. The Contracting Officer and the contractor may, by mutual consent, identify elsewhere in this contract specific information and/or categories of information which the Government will furnish to the Contractor or that the Contractor is expected to generate, which is confidential. Similarly, the Contracting Officer and the Contractor may, by mutual consent, identify such confidential information from time to time during the performance of the contract. Failure to agree will be settled pursuant to the Disputes clause.

4. If it is established elsewhere in this contract that information to be utilized under this contract or a portion thereof, is subject to the Privacy Act, the Contractor will follow the rules and procedures of disclosure set forth in the Privacy Act of 1974, 5 U.S.C. 552a, and implementing regulations and policies, with respect to systems of records determined to be subject to the Privacy Act.

5. Confidential information as defined in (H.2.1)(1) and (2) above, that is information or data of a personal nature about an individual, or proprietary information or data submitted by or pertaining to an institution or organization, shall not be disclosed without the prior written consent of the individual, institution or organization.

6. Written advance notice of at least 45 days will be provided to the Contracting Officer of the Contractor's intent to release findings of studies or research, which have the possibility of adverse effects on the public or the Federal agency, as described in (B) above. If the Contracting Officer does not pose any objections in writing within the 45-day period, the Contractor may proceed with disclosure. Disagreements not resolved by the Contractor and the Contracting Officer will be settled pursuant to the Disputes clause. The advance notice must be in the Contracting Officer's hands at least 45 days prior to disclosure, and any Contracting Officer objections must be in the Contractor's hands within 30 days of Contracting Officer receipt of the notice.

7. Whenever the contractor is uncertain with regard to the proper handling of material under the contract, or if the material in question is subject to the Privacy Act or is confidential information subject to the provisions of this clause, the Contractor should obtain a written determination from the Contracting Officer prior to any release, disclosure, dissemination or publication.

8. Contracting Officer determinations will reflect the results of internal coordination with appropriate program and legal officials.

9. The provisions of paragraph (5) of this clause shall not apply when the information is subject to conflicting or overlapping provisions in other Federal, State or local laws.

H.3 Clearance for Publication

No information furnished to or generated by the contractor in the performance of this contract shall be released to the public until it has been reviewed by the Government Project Officer for accuracy of factual data and interpretation. The Government shall have 90 calendar days after receipt of the manuscript or other written draft of the material to be released, to review, comment, and return to the contractor.

H.4 Care of Laboratory Animals

1. Before undertaking performance of any contract involving the use of laboratory animals, the contractor shall register with the Secretary of Agriculture of the United States in accordance with Section 6, Public Law 89-544, Laboratory Animal Welfare Act, August 24, 1966, as amended by Public Law 91-579, Animal Welfare Act of 1970, December 24, 1970. The contractor shall furnish evidence of such registration to the Contracting Officer.

2. The contractor shall acquire animals used in research and development programs from a dealer licensed by the Secretary of Agriculture, or from exempted sources in accordance with the Public Laws enumerated in (H.4.1), above, of this provision.

3. In the care of any live animals used or intended for use in the performance of this contract, the Contractor shall adhere to the principles enunciated in the Guide for Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, National Academy of Sciences (NAS)-National Research Council (NRC), and in the United States Department of Agriculture's (USDA) regulations and standards issued under the Public Laws enumerated in (H.4.1) above. In case of conflict between standards, the higher standard shall be used. Contractor reports on portions of the contract in which animals were used shall contain a certificate stating that the animals were cared for in accordance with the principles enunciated in the Guide for Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources, NAS-NRC, and/or in the regulations and standards as promulgated by the Agricultural Research Service, USDA, pursuant to the Laboratory Animal Welfare Act of August 24, 1966, as amended (Public Law 89-544 and Public Law 91-579).

   NOTE: The contractor may request registration of his facility and a current listing of licensed dealers from the Regional Office of the Animal and Plant Health Inspection Service (APHIS), USDA, for the region in which his research facility is located. The location of the appropriate APHIS Regional Office as well as information concerning this program may be obtained by contracting the Senior Staff Officer, Animal Care Staff, USDA/APHIS, Federal Center Building, Hyattsville, Maryland 20782.

H.5 Good Laboratory Practices (GLP)

In the performance of any nonclinical laboratory testing under this contract, the contractor shall adhere to the principles and procedures contained in FDA Regulation Part 58, entitled "Good Laboratory Practices." All nonclinical laboratory testing performed under this contract is subject to surveillance and inspection as required by the GLP Regulations and in accordance with the General Provisions of this contract entitled, "Inspection."

SECTION I - CONTRACT CLAUSES

CONTRACT CLAUSES FOR A COST-PLUS-FIXED-FEE CONTRACT

CLAUSES INCORPORATED BY REFERENCE (APRIL 1984)

This contract incorporates the following clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

I. FEDERAL ACQUISITION REGULATIONS (FAR) (48 CFR CHAPTER 1) CLAUSES

No.	FAR Clause No.	Title and Date
1.	52.203-1	Officials Not to Benefit (APRIL 1984)
2.	52.203-3	Gratuities (APRIL 1984)
3.	52.203-5	Covenant Against Contingent Fees (APRIL 1984)
4.	52.215-1	Examination of Records by Comptroller General (APRIL 1984)
5.	52.215-2	Audit-Negotiation (APRIL 1984)
6.	52.215-22	Price Reduction for Defective Cost or Pricing Data (APRIL 1984)
7.	52.215-24	Subcontractor Cost or Pricing Data (APRIL 1984)
8.	52.215-30	Facilities Capital Cost of Money (APRIL 1984)
9.	52.215-31	Waiver of Facilities Capital Cost of Money (APRIL 1984)
10.	52.216-7	Allowable Cost and Payment (APRIL 1984)
11.	52.216-8	Fixed Fee (APRIL 1984)
12.	52.219-8	Utilization of Small Business Concerns and Small Disadvantaged Business Concerns (APRIL 1984)
13.	52.219-13	Utilization of Women-Owned Small Businesses (APRIL 1984)
14.	52.220-3	Utilization of Labor Surplus Area Concerns (APRIL 1984)
15.	52.222-3	Convict Labor (APRIL 1984)
16.	52.222-20	Walsh-Healy Public Contracts Act (APRIL 1984)
17.	52.222-26	Equal Opportunity (APRIL 1984)
18.	52.222-35	Affirmative Action for Special Disabled and Vietnam Era Veterans (APRIL 1984)
19.	52.222-36	Affirmative Action for Handicapped Workers (APRIL 1984)
20.	52.223-2	Clean Air and Water (Over $100,000) (APRIL 1984)
21.	52.225-3	Buy American Act - Supplies (APRIL 1984)

CONTRACT CLAUSES FOR A COST-PLUS-FIXED-FEE CONTRACT (Incorporated by Reference) (APRIL 1984) -- Continued

22.	52.227-1	Authorization and Consent (APRIL 1984)

OR

(If this contract is for research and development; or involves both research and development work and supplies or services, and the research and development work is the primary purpose of the contract, the following clause is applicable):

22.	52.227-1	Authorization and Consent (APRIL 1984) - Alternate I (APRIL 1984)
23.	52.227-2	Notice and Assistance Regarding Patent and Copy-Right Infringement (APRIL 1984)

(If this clause is for experimental, developmental, or research work, the following clause is applicable):

24.	52.227-11	Patent Rights - Retention by the Contractor (Short Form) (APRIL 1984) NOTE: In accordance with FAR 27.303(a)(2), paragraph (e) is modified to include the requirements in FAR 27.303(a)(2)(i) thru (v). The frequency of reporting in (i) is annual.
25.	52.232-9	Limitation on Withholding of Payments (APRIL 1984)
26.	52.232-17	Interest (APRIL 1984)
27.	52.232-20	Limitation of Cost (APRIL 1984)
28.	52.232-23	Assignment of Claims (APRIL 1984)
29.	52.233-1	Disputes (APRIL 1984)
30.	52.242-1	Notice of Intent to Disallow Costs (APRIL 1984)
31.	52.243-2	Changes - Cost Reimbursement (APRIL 1984) - Alternate V (APRIL 1984)
32.	52.244-2	Subcontracts Under Cost-Reimbursement and Letter Contracts (APRIL 1984)
33.	52.244-5	Competition in Subcontracting (APRIL 1984)
34.	52.245-5	Government Property (Cost-Reimbursement, Time-and-Material, or Labor-Hour Contract) (APRIL 1984)
35.	52.246-9	Inspection of Research and Development (Short Form) (APRIL 1984)
36.	52.246-23	Limitation of Liability (APRIL 1984)
37.	52.249-6	Termination (Cost-Reimbursement) (APRIL 1984)
38.	52.249-14	Excusable Delays (APRIL 1984)

CONTRACT CLAUSES FOR A COST-PLUS-FIXED-FEE CONTRACT
(Incorporated by Reference) (APRIL 1984) -- Continued

II. DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATIONS (HHSAR) (48 CFR CHAPTER 3) CLAUSES

No.	HHSAR Clause No.	Title and Date
1.	352.202-1	Definitions (APRIL 1984) - Alternate I (APRIL 1984)
2.	352.208-70	Printing (APRIL 1984)
3.	352.227-1	Rights in Data (APRIL 1984)
4.	352.228-70	Required Insurance (APRIL 1984)
5.	352.232-9	Withholding of Contract Payments (APRIL 1984)
6.	352.233-70	Litigation and Claims (APRIL 1984)
7.	352.237-71	Services of Consultants (APRIL 1984)
8.	352.242-70	Notice to the Government of Delays (APRIL 1984)
9.	352.242-71	Final Decisions on Audit Findings (APRIL 1984)
10.	352.247-70	Foreign Travel (APRIL 1984)
11.	352.270-5	Key Personnel (APRIL 1984)
12.	352.270-6	Publication and Publicity (APRIL 1984)
13.	352.270-7	Paperwork Reduction Act (APRIL 1984)
14.	352.270-8	Advertising of Awards (APRIL 1984)

SECTION I - CONTRACT CLAUSES

CONTRACT CLAUSES INCLUDED IN FULL TEXT

Listed below are the reference number, title and date of all contract clauses that are attached hereto and made a part of this contract.

No.	FAR/HHSAR Clause No.	Title and Date
1.	FAR 52.230-3	Cost Accounting Standards (APRIL 1984)
2.	FAR 52.230-5	Disclosure and Consistency of Cost Accounting Practices (APRIL 1984)
3.	Prompt Payment Act	Late Payments to the Government (APRIL 1984)
4.	FAR 52.223-3	Protest After Award (JUNE 1985)
5.	HHSAR 392.232.72	Prohibition Against the Use of HHS Funds to Influence Legislation or Appropriations (APRIL 1984)

-Clause No. 1 COST ACCOUNTING STANDARDS (APR 1984)

COST ACCOUNTING STANDARDS (APR 1984)

(a) Unless the Cost Accounting Standards Board (CASB) has prescribed rules or regulations exempting the Contractor or this contract from standards, rules, and regulations promulgated pursuant to 50 U.S.C. App. 2168 (Pub. L. 91-379, August 15, 1970), the Contractor, in connection with this contract, shall—

(1) (National Defense Contracts Only) By submission of a Disclosure Statement, disclose in writing the Contractor's cost accounting practices as required by regulations of the CASB. The practices disclosed for this contract shall be the same as the practices currently disclosed and applied on all other contracts and subcontracts being performed by the Contractor and which contain a Cost Accounting Standards (CAS) clause. If the Contractor has notified the Contracting Officer that the Disclosure Statement contains trade secrets and commercial or financial information which is privileged and confidential, the Disclosure Statement shall be protected and shall not be released outside of the Government.

(2) Follow consistently the Contractor's cost accounting practices in accumulating and reporting contract performance cost data concerning this contract. If any change in cost accounting practices is made for the purposes of any contract or subcontract subject to CASB requirements, the change must be applied prospectively to this contract, and the Disclosure Statement must be amended accordingly. If the contract price or cost allowance of this contract is affected by such changes, adjustment shall be made in accordance with subparagraph (a)(4) or (a)(5) below, as appropriate.

(3) Comply with all CAS in effect on the date of award of this contract or, if the Contractor has submitted cost or pricing data, on the date of final agreement on price as shown on the Contractor's signed certificate of current cost or pricing data. The Contractor shall also comply with any CAS which hereafter becomes applicable to a contract or subcontract of the Contractor. Such compliance shall be required prospectively from the date of applicability to such contract or subcontract.

(4) (i) Agree to an equitable adjustment as provided in the Changes clause of this contract if the contract cost is affected by a change which, pursuant to (3) above, the Contractor is required to make to the Contractor's established cost accounting practices.

(ii) Negotiate with the Contracting Officer to determine the terms and conditions under which a change may be made to a cost accounting practice, other than a change made under other provisions of this paragraph 4; *provided*, that no agreement may be made under this provision that will increase costs paid by the United States.

(iii) When the parties agree to a change to a cost accounting practice, other than a change under (4)(i) above, negotiate an equitable adjustment as provided in the Changes clause of this contract.

(5) Agree to an adjustment of the contract price or cost allowance, as appropriate, if the Contractor or a subcontractor fails to comply with an applicable Cost Accounting Standard or to follow any cost accounting practice consistently and such failure results in any increased costs paid by the United States. Such adjustment shall provide for recovery of the increased costs to the United States together with interest thereon computed at the rate determined by the Secretary of the Treasury pursuant to Pub. L. 92-41, 85 Stat. 97, or 7 percent per annum, whichever is less, from the time the payment by the United States was made to the time the adjustment is effected.

(b) If the parties fail to agree whether the Contractor or a subcontractor has complied with an applicable CAS, rule, or regulation of the CASB and as to any cost adjustment demanded by the United States, such failure to agree shall be a dispute concerning a question of fact within the meaning of the Disputes clause of this contract.

(c) The Contractor shall permit any authorized representatives of the agency head, of the CASB, or of the Comptroller General of the United States to examine and make copies of any documents, papers, or records relating to compliance with the requirements of this clause.

(d) The Contractor shall include in all negotiated subcontracts which the Contractor enters into, the substance of this clause, except paragraph (b), and shall require such inclusion in all other subcontracts, of any tier, including the obligation to comply with all CAS in effect on the subcontract's award date or if the subcontractor has submitted cost or pricing data, on the date of final agreement on price as shown on the subcontractor's signed Certificate of Current Cost or Pricing Data. This requirement shall apply only to negotiated subcontracts in excess of $100,000 where the price negotiated is not based on—

(1) Established catalog or market prices of commercial items sold in substantial quantities to the general public; or

(2) Prices set by law or regulation, and except that the requirement shall not apply to negotiated subcontracts otherwise exempt from the requirement to include a CAS clause by reason of 331.30(b) of Title 4, Code of Federal Regulations (4 CFR 331.30(b)).

Note (1): New CAS shall be applicable to both national defense and nondefense CAS-covered contracts upon award of a new national defense CAS-covered contract containing the new Standard. The award of a new nondefense CAS-covered contract shall not trigger application of new CAS.

Note (2): Subcontractors shall be required to submit their Disclosure Statements to the Contractor. However, if a subcontractor has previously submitted its Disclosure Statement to a Government Administrative Contracting Officer (ACO), it may satisfy that requirement by certifying to the Contractor the date of the Statement and the address of the ACO.

Note (3): In any case where a subcontractor determines that the Disclosure Statement information is privileged and confidential and declines to provide it to the Contractor or higher tier subcontractor, the Contractor may authorize direct submission of that subcontractor's Disclosure Statement to the same Government offices to which the Contractor was required to make submission of its Disclosure Statement. Such authorization shall in no way relieve the Contractor of liability as provided in paragraph (a)(5) of this clause. In view of the foregoing and since the contract may be subject to adjustment under this clause by reason of any failure to comply with rules, regulations, and Standards of the CASB in connection with covered subcontracts, it is expected that the Contractor may wish to include a clause in each such subcontract requiring the subcontractor to appropriately indemnify the Contractor. However, the inclusion of such a clause and the terms thereof are matters for negotiation and agreement between the Contractor and the subcontractor, provided that they do not conflict with the duties of the Contractor under its contract with the Government. It is also expected that any subcontractor subject to such indemnification will generally require substantially similar indemnification to be submitted by its subcontractors.

Note (4): If the subcontractor is a business unit which, pursuant to 4 CFR 332 is entitled to elect modified contract coverage and to follow Standards 401 and 402, the clause at 52.230-5, "Disclosure Consistency of Cost Accounting Practices," of the Federal Acquisition Regulation shall be inserted in lieu of this clause.

Note (5): The terms defined in 4 CFR 331.20 shall have the same meanings herein. As there defined, "negotiated subcontract" means any subcontract except a firm-fixed-price subcontract made by a Contractor or subcontractor after receiving offers from at least two persons not associated with each other or with such Contractor or subcontractor, providing (1) the solicitation to all competitors is identical, (2) price is the only consideration in selecting the subcontractor from among the competitors solicited, and (3) the lowest offer received in compliance with the solicitation from among those solicited is accepted.

(End of clause)

(R 7-104.83(a) 1975 FEB)

(R 1-3.1204-1(a)(1))

(R 1-3.1204-2(a))

Clause No. 2 DISCLOSURE AND CONSISTENCY OF COST ACCOUNTING PRACTICES (APR 1984)

(a) The Contractor, in connection with this contract, shall—

(1) Comply with the requirements of 4 CFR Parts 401, Consistency in Estimating, Accumulating, and Reporting Costs, and 402, Consistency in Allocating Costs Incurred for the Same Purpose, in effect on the date of award of this contract.

(2) (National Defense Contracts Only) If it is a business unit of a company required to submit a Disclosure Statement, disclose in writing its cost accounting practices as required by regulations of the Cost Accounting Standards Board (CASB). If the Contractor has notified the Contracting Officer that the Disclosure Statement contains trade secrets and commercial or financial information which is privileged and confidential, the Disclosure Statement shall be protected and shall not be released outside of the Government.

Note (1): Subcontractors shall be required to submit their Disclosure Statements to the Contractor. However, if a subcontractor has previously submitted its Disclosure Statement to a Government Administrative Contracting Officer (ACO), it may satify that requirement by certifying to the Contractor the date of the Statement and the address of the Contracting Officer.

Note (2): In any case where a subcontractor determines that the Disclosure Statement information is privileged and confidential and declines to provide it to the Contractor or higher tier subcontractor, the Contractor may authorize direct submission of the subcontractor's Disclosure Statement to the same Government offices to which the Contractor was required to make submission of its Disclosure Statement. Such authorization shall in no way relieve the Contractor of liability if it or a subcontractor fails to comply with an applicable Cost Accounting Standard (CAS) or to follow any practice disclosed pursuant to this paragraph and such failure results in any increased costs paid by the United States. In view of the foregoing and since the contract may be subject to adjustment under this clause by reason of any failure to comply with rules, regulations, and Standards of the CASB in connection with covered subcontracts, it is expected that the Contractor may wish to include a clause in each such subcontract requiring the subcontractor to appropriately indemnify the Contractor. However, the inclusion of such a clause and the terms thereof are matters for negotiation and agreement between the Contractor and subcontractor, provided that they do not conflict with the duties of the Contractor under its contract with the Government. It is also expected that any subcontractor subject to such indemnification will generally require substantially similar indemnification to be submitted by its subcontractors.

Note (3): The terms defined in 4 CFR 331.20 shall have the same meanings in this clause. As there defined, "negotiated subcontract" means any subcontract except a firm-fixed-price subcontract made by a Contractor or subcontractor after receiving offers from at least two persons not associated with each other or such Contractor or subcontractor, providing (1) the solicitation to all competitors is identical, (2) price is the only consideration in selecting the subcontractor from among the competitors solicited, and (3) the lowest offer received in compliance with the solicitation from among those solicited is accepted.

(3) (i) Follow consistently the Contractor's cost accounting practices. A change to such practices may be proposed, however, by either the Government or the Contractor, and the Contractor agrees to negotiate with the Contracting Officer the terms and conditions under which a change may be made. After the terms and conditions under which the change is to be made have been agreed to, the change must be applied prospectively to this contract, and the Disclosure Statement, if affected, must be amended accordingly.

* (ii) The Contractor shall, when the parties agree to a change to a cost accounting practice and the Contracting Officer has made the finding required in 332.51 of the CASB's regulations, negotiate an equitable adjustment as provided in the Changes clause of this contract. In the absence of the required finding, no agreement may be made under this contract clause that will increase costs paid by the United States.

(4) Agree to an adjustment of the contract price or cost allowance, as appropriate, if the Contractor or a subcontractor fails to comply with the applicable CAS or to follow any cost accounting practice, and such failure results in any increased costs paid by the United States. Such adjustment shall provide for recovery of the increased costs to the United States together with interest thereon computed at the rate determined by the Secretary of the Treasury pursuant to Pub. L. 92-41, 85 Stat. 97, or 7 percent per annum, whichever is less, from the time the payment by the United States was made to the time the adjustment is effected.

(b) If the parties fail to agree whether the Contractor has complied with an applicable CAS, rule, or regulation of the CASB and as to any cost adjustment demanded by the United States, such failure to agree shall be a dispute within the meaning of the Disputes clause of this contract.

Clause No. 2 continued

(c) The Contractor shall permit any authorized representatives of the agency head, of the CASB, or of the Comptroller General of the United States to examine and make copies of any documents, papers, and records relating to compliance with the requirements of this clause.

(d) The Contractor shall include in all negotiated subcontracts, which the Contractor enters into, the substance of this clause, except paragraph (b), and shall require such inclusion in all other subcontracts of any tier, except that—

(1) If the subcontract is awarded to a business unit which pursuant to Part 331 is required to follow all CAS, the clause entitled "Cost Accounting Standards," set forth in 331.50 of the CASB's regulations shall be inserted in lieu of this clause; or

(2) This requirement shall apply only to negotiated subcontracts in excess of $100,000 where the price negotiated is not based on—

(i) Established catalog or market prices of commercial items sold in substantial quantities to the general public; or

(ii) Price set by law or regulation.

(3) The requirement shall not apply to negotiated subcontracts otherwise exempt from the requirement to include a CAS clause by reason of 331.30(b) of the CASB's regulations.

(End of clause)

Clause No. _3_ **Late Payments to the Government**

Late payment of debts owed the Government by the contractor, arising from whatever cause, under this contract/order shall bear interest at a rate or rates to be established in accordance with the Treasury Fiscal Requirements Manual. For purposes of this provision, late payments are defined as payments received by the Government more than 30 days after the contractor has been notified in writing by the Contracting Officer of:

a. The basis of the indebtedness.
b. The amount due.
c. The fact that interest will be applied if payment is not received within 30 days from the date of mailing of the notice.
d. The approximate interest rate that will be charged.

Clause NO. 4

Protest After Award (June 1985)

(a) Upon receipt of a notice of protest (as defined in 33.101 of the FAR) the Contracting Officer may, by written order to the Contractor, direct the Contractor to stop performance of the work called for by this contract. The order shall be specifically identified as a stop-work order issued under this clause. Upon receipt of the order, the Contractor shall immediately comply with its terms and take all reasonable steps to minimize the incurrence of costs allocable to the work covered by the order during the period of work stoppage. Upon receipt of the final decision in the protest, the Contracting Officer shall either—

(1) Cancel the stop-work order; or

(2) Terminate the work covered by the order as provided in the Default, or the Termination for Convenience of the Government, clause of this contract.

(b) If a stop-work order issued under this clause is canceled either before or after a final decision in the protest, the Contractor shall resume work. The Contracting Officer shall make an equitable adjustment in the delivery schedule or contract price, or both, and the contract shall be modified, in writing, accordingly, if—

(1) The stop-work order results in an increase in the time required for, or in the Contractor's cost properly allocable to, the performance of any part of this contract; and

(2) The Contractor requests an adjustment within 30 days after the end of the period of work stoppage, *provided*, that if the Contracting Officer decides the facts justify the action, the Contracting Officer may receive and act upon the request at any time before final payment under this contract.

(c) If a stop-work order is not canceled and the work covered by the order is terminated for the convenience of the Government, the Contracting Officer shall allow reasonable costs resulting from the stop-work order in arriving at the termination settlement.

(d) If a stop-work order is not canceled and the work covered by the order is terminated for default, the Contracting Officer shall allow, by equitable adjustment or otherwise, reasonable costs resulting from the stop-work order.

(e) The Government's rights to terminate this contract at any time are not affected by action taken under this clause.

Clause No. 5 Prohibition Against Use of FDA Funds to Influence Legislation or Appropriations (APRIL 1984)

No part of any funds under this contract shall be used to pay the salary or expenses of any Contractor, or agent acting for the Contractor, to engage in any activity designed to influence legislation or appropriations pending before the Congress.

SECTION J

BIBLIOGRAPHY

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AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT ID CODE

PAGE 1 OF PAGES 1

2. AMENDMENT/MODIFICATION NO. 1

3. EFFECTIVE DATE Upon Execution

4. REQUISITION/PURCHASE REQ. NO.

5. PROJECT NO. (If applicable)

6. ISSUED BY CODE

DHHS/Public Health Service
Food and Drug Administration, HFA-531
5600 Fishers Lane, Park Building, Rm. 3-32
Rockville, Maryland 20857

7. ADMINISTERED BY (If other than Item 6) CODE

8. NAME AND ADDRESS OF CONTRACTOR (No., street, county, State and ZIP Code)

Batteile Memorial Institute
Columbus Division
505 King Avenue
Columbus, Ohio 43201-2693

CODE

FACILITY CODE

(✓) 9A. AMENDMENT OF SOLICITATION NO.

9B. DATED (SEE ITEM 11)

X 10A. MODIFICATION OF CONTRACT/ORDER NO. 223-86-2095

10B. DATED (SEE ITEM 13) 9/25/86

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offers ☐ is extended, ☐ is not extended.

Offers must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended, by one of the following methods:

(a) By completing Items 8 and 15, and returning ______ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted; or (c) By separate letter or telegram which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted, such change may be made by telegram or letter, provided each telegram or letter makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNTING AND APPROPRIATION DATA (If required)

13. THIS ITEM APPLIES ONLY TO MODIFICATIONS OF CONTRACTS/ORDERS, IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

(✓)	
	A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: (Specify authority) THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
	B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIFIED TO REFLECT THE ADMINISTRATIVE CHANGES (such as changes in paying office, appropriation date, etc.) SET FORTH IN ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(b).
X	C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF: Mutual agreement of both parties within the Scope of the contract
	D. OTHER (Specify type of modification and authority)

E. IMPORTANT: Contractor ☐ is not, ☒ is required to sign this document and return 3 copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION (Organized by UCF section headings, including solicitation/contract subject matter where feasible.)

The purpose of this modification is to amend the Key Personnel clause to reflect the new Principal Investigator.

Contract 223-86-2095 is hereby modified as follows:

1. Under paragraph G.2, Key Personnel, the name "Dr. Gillian Haggerty" is deleted and the name "Dr. Gary Freeman" is substituted therefor.

The contract amount, Scope of Work, and expiration date are not changed as a result of this modification.

Except as provided herein, all terms and conditions of the document referenced in Item 9A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER (Type or print)
H. MICHAEL SEWELL
CONTRACTING OFFICER

15B. CONTRACTOR/OFFEROR Sewell

15C. DATE SIGNED JUNE 10, 1987

16A. NAME AND TITLE OF CONTRACTING OFFICER (Type or print)
Thomas H. Vargo

16B. UNITED STATES OF AMERICA

16C. DATE SIGNED 6/22/87

Battelle
Columbus Division
505 King Avenue
Columbus, Ohio 43201-2693
Telephone (614) 424-6424
Telex 24-5454

October 16, 1987

Dr. Thomas Sobotka
U.S. Food and Drug Administration
200 C Street, SW
HFF-162
Washington, DC 20204
Contract no.: 223-86-2095

Dear Tom:

Enclosed is a report which details the HPLC methods we have standardized as well as critical control values from a group of five animals. Based on the results we believe that the proposed methods are more than adequate for the purposes intended and, moreover, appear to be reproducible from day to day. We are continuing to develop methods for the receptor analysis portion of the contract. This should not pose a problem since receptor binding is not an integral part of the model development section of the study.

I am in the process of scheduling a meeting with the quality assurance people at Battelle to finalize the requirements for the GLP phase of the contract.

If you can circulate the enclosed material to the PAG for their review and comments, the methods can then be converted into SOPs and actual experimentation can begin.

I have sent a copy of the enclosed to Tom Vargo's office. Please call me if you have any questions.

Very truly yours,

Gary B. Freeman

Gary B. Freeman, Ph.D.
Chemical Safety and Drug
Development Section

REPORT

Contract No. 223-86-2095

on

REPORT ON HPLC METHODS FOR THE DETERMINATION OF REGIONAL BRAIN NEUROTRANSMITTER CONTENT FOR THE STUDY OF DIETARY AMINO ACIDS AND BRAIN FUNCTION

October 16, 1987

BATTELLE
Columbus Division
505 King Avenue
Columbus, Ohio 43201

INTRODUCTION

The initial phase of the Dietary Amino Acids and Brain Function project (223-86-2095) will involve determination of brain monoamine levels and metabolite concentrations in order to select the most appropriate animal model for studying dietary aspartame (APM) and neurotransmitter function. Methods using high pressure liquid chromatography with electrochemical detection for the quantitation of catecholamine and indoleamine compounds were standardized with tissue from Fischer 344 male rats. Untreated animals were sacrificed and brains quickly removed. Seven brain regions (hypothalamus, cerebellum, pons/medulla, hippocampus, striatum, cortex and midbrain/thalamus) were dissected and tissue frozen for later analysis. Because of the various brain regions and number of compounds investigated, two discrete systems were dedicated; one for the indoleamines and the other for the catecholamines. With the indoleamine system, we were able to quantify serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), 5-hydroxy-DL-tryptophan (5-HTP), 4-hydroxy-3-methoxyphenylacetic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC). The catecholamine system provided quantitation of norepinephrine (NE), epinephrine (EPI), dopamine (DA), DL-β-3,4-dihydroxyphenylalanine (DOPA) and the internal standard, 3,4-dihydroxybenzylamine hydrobromide (DBA). A complete method description for these analyses has been included. Individual animal data and means of each compound in the different brain regions are supplied in tubular form. Additional data which demonstrate the day to day reproducibility of the methods (external standards) has also been provided. The results represent data from 5 animals whose brains were analyzed under the most optimum conditions that were selected after months of methods standardization.

METHOD

Detailed methods for the determination of neurotransmitter and metabolite concentrations are provided on pages 2-15.

I. ANALYSIS OF CATECHOLAMINES BY HPLC FOR STUDY OF THE EFFECTS OF ASPARTAME ON BRAIN NEUROCHEMISTRY

A. MATERIALS

Item	Company	Catalog #
Perchloric acid (69-72%)	Baker	9652-1
Ascorbic acid sodium salt	Sigma	A7631
Trizma base	Sigma	T1503
Sodium phosphate dibasic	Sigma	S0876
Octyl sulfate sodium salt	Sigma	04003
Methanol	Burdick & Jackson	230
Alumina activity grade I (WN3)	Sigma	A9003
STANDARDS		
NE - (-)arterenol bitartrate salt	Sigma	A9512
EPI - (-)epinephrine (+) bitartrate	Sigma	E4375
DOPAC - 3,4-dihydroxyphenylacetic acid	Sigma	D9128
DA - 3-hydroxytyramine hydrochloride	Sigma	H8502
DOPA - DL-β-3,4-dihydroxyphenylalanine	Sigma	D9503
DBA - 3,4-dihydroxybenzylamine hydrobromide	Sigma	D9128

B. PREPARATION OF REAGENTS AND STANDARDS

0.2 N - perchloric acid with 0.002% ascorbic acid:

- 1.72 ml of stock (70% perchloric) per 100 ml distilled H_2O
- 0.002 g ascorbic acid per 100 ml distilled H_2O

0.5 M - Tris buffer:

M.W. = 121.1
60.5 g/liter
pH to 8.4

Mobile Phase (for DOPA separation):

50 mM Na phosphate dibasic M.W. = 142.0 7.1 g per liter
pH to 3.25 with phosphoric acid
Add 50 mg octyl sulfate/liter
Filter (0.2 μm)
Degas
Add 80 mls of degassed MEOH (20 min) per liter of mobile phase

Catecholamine Standard Stock Solution: (store refrigerated in 1.5 ml microfuge tubes)

	M.W. of complex	mg/100 ml perchloric acid with 0.002% ascorbate	ng/ml	pmol/ml	÷	pmol/ml free base
*NE	319.3	48.2	482000	1509552	1.887	799975
*EPI	333.3	48.5	485000	1455146	1.819	799970
DOPAC	168.2	13.5	135000	802616	1.0	802616
*DA	189.6	18.8	188000	991561	1.238	800938
DOPA	197.2	15.8	158000	801217	1.0	801217

Internal Standard Stock Solution: (store refrigerated in 1.5 ml microfuge tubes)

	M.W.	mg/100 ml perchloric acid with 0.002% ascorbate	ng/ml	pmol/ml	÷	pmol/ml free base
*DBA	220.1	28.6	286000	1299409	1.559	833489

*molecular weight of free base:
NE = 169.2
EPI = 183.2
DA = 153.2
DBA = 141.1

Catecholamine Standard Working Solutions (80, 40, 20, 10 pmol): From the stock solution of the catechols take 40 μl and dilute to 100 ml with 0.2N-PCA with 0.002% ascorbate. When a 250 μl aliquot is taken it is equivalent to ~ 80 pmol of each compound (NE - 79.998, EPI - 79.997, DOPAC - 80.262, DA - 80.094, DOPA - 80.122). Further dilutions are made in the following way:

40 pmol: 1 ml of 80 pmol plus 1 ml of 0.2N-PCA with ascorbate
20 pmol: 0.5 ml of 80 pmol plus 1.5 ml of 0.2N-PCA with ascorbate
10 pmol: 0.25 ml of 80 pmol plus 1.75 ml of 0.2N-PCA with ascorbate

Internal Standard Working Solution: From DBA stock, take 60 μl and dilute to 10 ml with 0.2N-PCA with ascorbate. The addition of 10 μl to all tubes is equivalent to ~50 pmol (DBA - 50.009).

External Standard Solution: For checking of instrument each day. From the catecholamine stock take 12.5 μl and from the DBA stock take 12.0 μl. Combine the two aliquots and dilute in 50 ml of 0.2N-PCA with ascorbate. An injection of 50 μl is equivalent to 10 μmol.

C. HPLC CONDITIONS

Stationary phase: LC-18, 5 μ, 25 cm x 4.6 mm Supelcosil column with LC-18 Supelguard guard column and filter (2 μm)
Solvent delivery system: Waters Model 6000A pump
Flow rate: 1.35 ml per min
Detector: LC4B/17A electrochemical detector (Bioanalytical Systems, Inc.)
Potential: 0.65 V versus an Ag/AgCl reference electrode

Sensitivity: 10 NaV
Injection System: Waters Intelligent Sample Processor (WISP) (Model 712)
Data Reduction: Altex Data Integrator (Model C-RIA).

Integrator Parameters

```
CAL PM       8
WIDTH       12
SLOPE     1000
DRIFT        0
MIN AR       0
T-BDL        0
LOCK         0
STP TM      20
ATTEN       10
SPEED        5
METHOD    1041
SPL WT     100
IS WT        1


TIME-P       8
     MAX    10

     #     TIME      NAME      DATA

     1      0        LOCK        0
     2       3.5     LOCK        0
     3     11        ATTN        9
```

D. REGIONAL DISSECTION OF RAT BRAIN AND TISSUE PREPARATION

1. Male rats (Sprague-Dawley or Fischer 344, 8-12 weeks of age) are killed by decapitation and the brains carefully removed and placed in 0.9% saline. The actual sacrifice and dissection of all animals will be done in a necropsy room located in the separate animal care facility. Each brain is placed ventral side up on an ice-cooled petri dish. The optic chiasm which delimits the anterior part of the hypothalamus is noted. The hypothalamus is scooped out by making a circular cut around the perimeter of the structure. The brain is turned over and the cerebellum is teased from the dorsal surface of the pons/medulla. The pons/medulla is then cut at a level up to the colli-culi. The hippocampus and striatum are exposed by gently folding back the cortex. The hippocampus is dissected bilaterally by peeling it back. The striatum which contains

the putamen caudate nuclei and the globus pallidus is dissected bilaterally with the external walls of the lateral ventricle as its internal limit and the corpus callosum as its external limit. The cortex with the corpus callosum as its internal limit is removed bilaterally. This is done to avoid including remaining portions of striatum. The midbrain (which includes thalamic and subthalamic structures) is separated from the rest of the brain. Each region as it is dissected is placed in a 1.5 ml Eppendorf microfuge tube and immediately frozen on dry ice. The cortex, striatum and hippocampus are separated into right and left halves and placed into individual microfuge tubes. The cerebellum, pons/medulla and midbrain/thalamus are bisected and each half placed in a separate tube. At this point they can be frozen (-80°C) for use at a later time or homogenized in 0.2 N-perchloric acid-containing 0.002 % wt/vol ascorbic acid using a tissue sonicator (Branson 200) that is equipped with a 1/8" stepped microtip. Tissue weighing 100 mg or less will be homogenized in 400 µl of 0.2 N PCA while tissue in the range of 100-150 mg will be homogenized at 4 µl per mg tissue. Due to the concentration of neurotransmitters and metabolites in striatum and midbrain/thalamus, these 2 regions will be homogenized at twice the volume (800 µl).

2. Aliquots of the supernatant are taken for the indoleamine (100 µl) (see II. ANALYSIS OF INDOLEAMINES) and protein (50 µl) (see III. PROTEIN DETERMINATIONS) analyses.

3. To 250 µl of the remaining homogenate, an internal standard (3,4-dihydroxybenzylamine) equivalent to 50 pmol is added to each sample.

4. A standard curve is run along with the samples and treated similarly.

5. Add 10 mg of alumina to the tubes. The alumina is stored covered in an oven or stored in a dessicator and heated up the night before.

6. The catecholamines (EPI, NE, DA, DOPAC, DOPA) are adsorbed on alumina by adding 1.25 ml of 0.5 M-Tris buffer, pH 8.4.

7. The tubes are placed in a test tube rack, secured and are shaken for 15 min using a Burrell Model 75 wrist action shaker and the alumina allowed to settle for 5 min.

8. The buffer is aspirated and the alumina is washed once with water and shaken for 5 min.

9. Catecholamines are eluted from the alumina by adding 100 µl of 0.2 M-perchloric acid containing 0.002% wt/vol ascorbic acid.

10. Samples are vortexed and then shaken for 10 min.

11. After centrifugation at 15000 rpm for 10 min in an Eppendorf Centrifuge Model 5415 (Brinkman), the supernatant is injected onto an HPLC via a WISP 712 autoinjector.

II. ANALYSIS OF INDOLEAMINES BY HPLC FOR INVESTIGATION OF ASPARTAME EFFECTS ON BRAIN NEUROCHEMISTRY

A. MATERIALS (additional)

Item	Company	Catalog #
Citric acid	Sigma	C0759
STANDARDS		
5-HTP - 5-hydroxyl-DL-tryptophan	Sigma	H8127
5-HT - 5-hydroxytryptamine creatine sulfate complex	Sigma	H7752
5-HIAA - 5-hydroxyindole acetic acid	Sigma	H8876
HVA - 4-hydroxy-3-methoxy-phenylacetic acid	Sigma	H1252

B. PREPARATION OF REAGENTS AND STANDARDS

Mobile Phase:

0.1 M - citric acid M.W. = 192.13 19.21 g/liter
0.2 M - dibasic sodium phosphate M.W. = 142.0 28.4 g/liter
To adjust to pH 4.6 add in the following manner
500 ml citric acid
435 ml dibasic sodium phosphate
Then dilute 1:1 with dh20
Methanol is added at 15% just before use.

External Standard Stock Solution: Each compound is added to the same container to make the stock solution of standards. Aliquots of the stock standard are refrigerated in 1.5 ml microfuge tubes.

	M.W. of complex	mg/100 ml perchloric acid with 0.002% ascorbate	ng/ml	pmol/ml	pmol/ml free base
*5-HT	387.4	85.1	851000	2196696 ÷ 2.199	998952
5-HIAA	191.2	38.2	382000	1997908 ÷ 1.0	1997908
5-HTP	220.2	22.0	220000	999092 ÷ 1.0	999092
HVA	182.0	18.2	182000	1000000 ÷ 1.0	1000000
DOPAC	168.2	16.8	168000	998811 ÷ 1.0	998811

*M.W. of free base = 176.2

External Standard Curve: From the stock solution, a 1:50 dilution is made. From this dilution, 12.5, 25, 50, or 100 μl are placed into 10 ml volumetric flasks and diluted to 10 ml with 0.2 N-PCA with 0.002% ascorbic acid. After injection of 50 μl of this working standard, the 4 separate standard solutions correspond to 1.25, 2.5, 5 and 10 pmol of 5-HTP, DOPAC, 5-HT and HVA and 2.5, 5, 10 and 20 pmol of 5-HIAA, respectively.

C. HPLC CONDITIONS

Stationary phase: LC-18, 5 µ, 25 cm x 4.6 mm Supelcosil column with LC-18 Supelguard column and filter (2 µm).

Solvent delivery system: PM-11 pump (Bioanalytical Systems, Inc.)

Flow rate: 1.30 ml/min

Detector: LC4A Amperometric detector (Bioanalytical Systems, Inc.)

Potential: 0.65 V versus an Ag/AgCl reference electrode

Sensitivity: 10 Na/V

Injection system: Rheodyne injection valve (Model 7125) with 50 µl loop size

Data Reduction: Hewlett Packard Integrator (Model 3390A).

<u>Integrator Parameters</u>

```
RUN PRMTRS
ZERO =       0
ATT 2↑ =     10
CHT SP =     0.5
PK WD =      0.64
THRSH =      7
AR REJ =     0

RPRT OPTNS

     2.  RF UNC PKS =     0.0000E+00
     3.  MUL FACTOR =     1.0000E+00
     4.  PK HEIGHT MODE  .    YES
     5.  EXTEND RT             NO
     6.  RPRT UNC PKS          NO

TIME TBL

      3.50 PK WD    = 0.16
      3.50 ATT 2↑   = 8
      8.50 ATT 2↑   = 10
     13.00 ATT 2↑   = 8
     18.00 STOP

CALIB TBL

     EMPTY
```

D. TISSUE PREPARATION

1. The 100 μl aliquot of the homogenate is spun at 15,000 rpm for 10 min and injected into the HPLC (50 μl injection volume). Samples are kept refrigerated until injection.

III. PROTEIN DETERMINATIONS (LOWRY METHOD) ON BRAIN TISSUE SAMPLES FOR STUDY OF THE EFFECTS OF ASPARTAME ON BRAIN NEUROCHEMISTRY

A. REAGENTS

1. 0.1 N Sodium Hydroxide (NaOH)
   Accurately weigh 2g NaOH, place in a 500 ml volumetric flask and QS to the mark with deionized water.

2. 2% Sodium Carbonate (Na_2CO_3)
   Accurately weigh 10.0g of Sodium Carbonate and dissolve in 500 ml of 0.1 N NaOH

3. 2% Sodium Tartrate
   Accurately weigh 2.0g Na Tartrate, place in a 100 ml volumetric flask and QS to the mark with deionized water.

4. 1% Cupric Sulfate ($CuSO_4 \cdot 5H_2O$)
   Accurately weigh 1.0g Cupric Sulfate · $5H_2O$, place in a 100 ml volumetric flash and QS to the mark with deionized water.

5. Undiluted Folins Reagent

6. 0.2N Perchloric Acid (PCA) with 0.002% Ascorbic Acid

   1.72 ml of 70% perchloric acid and 0.002g ascorbic acid per 100 ml in deionized water.

B. STANDARDS

Note: Keep all standards frozen.

1. Prepare Bovine Serum Albumin (BSA) Stock Solution:

   Accurately weigh 10g of BSA and dissolve in deionized water to make 100 ml. This is equal to 1000 μg/10 μl.

2. Make a 1 in 10 dilution of the 1000 μg/10μl stock solution to give 100 μg/10 μl in deionized water.

3. Prepare BSA Working Standards as follows:

BSA Conc. (µg/10µl)	µl of 100 µg/10 µl Stock	µl deionized Water
5	50	950
10	100	900
15	150	850
20	200	800
25	250	750
30	300	700

C. ASSAY

1. Turn spectrophotometer on.

2. Prepare Reagent A (fresh for the assay)

   a. 50 volumes 2% Na_2CO_3 in 0.1N NaOH
   b. Add 0.5 volumes of 2% sodium tartrate to a. and mix
   c. Add 0.5 volumes of 1% $CuSO_4 \cdot 5H_2O$, add to the solution prepared in b. and mix.

3. In microcentrifuge tubes, make a 2 in 10 dilution of the tissue homogenate from the hypothalamus and striatum brain sections using 0.2N PCA with 0.002% ascorbic acid. Similarly make a 1 in 10 dilution of the tissue homogenate from the remaining brain sections.

4. Add triplicate 10 µl aliquots of each BSA working standard and duplicate 10 µl aliquots of deionized water for the blanks to individual 5 ml borosilicate glass disposable tubes.

5. Add triplicate 10 µl aliquots of each 1 in 10 or 2 in 10 dilution of tissue homogenate from step 3 to individual tubes, and add a single 10 µl aliquot of 0.2N PCA with 0.002% ascorbic acid to another tube.

6. Add 1.0 ml of Reagent A to each of the 10 µl aliquots prepared in steps 4 and 5 above. Vortex briefly immediately upon addition to each tube and let stand at room temperature for 10 minutes.

7. Add 50 µl undiluted Folins Reagent. Vortex briefly immediately upon addition to each tube and let stand at room temperature for 30 minutes.

8. Read the absorbance of the samples in a UV-VIS recording spectrophotometer (Shimadzu UV-160) in the quantitative mode at 750 nm as follows (see operating in quantitative mode, 4-46- 4-50 of Shimadzu UV-160 manual):

   a. Place the deionized water blanks in the reference and sample 1 cm microcuvettes and zero the instrument. Read the standards.

b. Place the PCA blank in the sample microcuvette and zero the instrument. Read the samples.

9. a. Dilution Correction:

In order to correct for the dilutions of tissue homogenate made in Step 3, multiply the concentration obtained for the hypothalamus and striatum sections by 5 and for the remaining sections by 10 to obtain the μg protein in 10 μl tissue homogenate.

b. Calculations:

The protein concentration for each sample is converted to mg protein by the following calculations.

Catecholamines

Sample conc. (from 9a) x 25 = protein concentration/250 μl sample.

Then, protein conc./250 μl sample x 0.5 = μg protein/50 μl injection sample.

Finally, $\frac{\text{μg protein/50 μl}}{1000}$ = mg protein/50 μl injection sample.

Indoleamines

Sample conc. (from 9a) x 5 = μg protein/50 μl injection sample.

Then, $\frac{\text{μg protein/50 μl}}{1000}$ = mg protein/50 μl injection sample.

RESULTS

Region specific catecholamine and indoleamine concentrations for individual animals are presented in Tables A-G. A summary table of these values in the seven specific brain areas is found in Table H. Extreme values were deleted from the means in the summary table by use of the Q-test at the 0.05 level. Daily critical values of a representative standard (5 pmole) from the indoleamine method are listed in Table I while values for a 20 pmole internal standard from the catecholamine method are presented in Table J. Since the internal standards are run through the assay and recoveries may vary, an external standard (10 pmole) was run twice each day to monitor any major fluctuations in the system (Table K). The concentration of DBA was the same (50 pmole) in all catecholamine internal standards and daily means are shown in Table L. Representative chromatograms from the indoleamine and catecholamine methods are also provided (Figures 1-3).

TABLE A. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Hypothalamus

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA	HVA
14-1-1	115.65*	22.46	8.30	9.37	25.98	--
15-1-1	116.97	7.91	8.26	16.32	29.63	--
16-1-1	116.98	43.03	8.35	20.91	28.34	--
17-1-1	112.59	45.68	8.67	21.61	35.48	4.15
18-1-1	110.89	29.40	7.05	17.80	33.36	--

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE B. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Cerebellum

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA.
14-2-3	19.65*	--	0.41	0.77	1.59
15-2-3	22.78	0.75	0.58	2.11	3.54
16-2-3	17.02	--	0.34	0.95	2.47
17-2-3	18.13	--	0.48	0.95	2.45
18-2-3	15.38	--	0.54	0.82	2.30

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid

TABLE C. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Pons/Medulla

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA	HVA
14-3-5	39.56*	4.90	1.85	6.82	7.80	0.76
15-3-5	33.53	5.36	2.85	17.53	18.77	--
16-3-5	32.65	5.40	2.19	14.72	16.85	2.43
17-3-5	59.28	7.79	2.90	21.28	29.97	5.34
18-3-5	27.63	4.72	2.01	12.59	21.27	1.32

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE D. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Hippocampus

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA
14-4-7	18.84*	--	0.52	5.29	11.45
15-4-7	23.53	--	0.68	9.26	19.84
16-4-7	29.98	2.59	1.29	9.85	23.79
17-4-7	30.36	--	0.78	9.22	25.78
18-4-7	28.85	3.77	2.16	9.98	30.80

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid

TABLE E. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Striatum

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA	HVA
14-5-9	--	351.69	113.29	3.21	12.21	35.58
15-5-9	2.02*	351.69	97.53	8.85	23.48	53.84
16-5-9	--	221.02	67.97	9.70	26.22	44.87
17-5-9	--	489.75	123.64	6.05	26.77	52.97
18-5-9	--	423.63	87.81	9.14	27.73	46.95

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE F. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Cortex

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA	HVA
14-6-11	19.10*	1.50	0.88	3.40	6.74	--
15-6-11	15.37	11.22	2.35	6.39	9.33	--
16-6-11	14.99	--	0.78	6.41	11.85	0.18
17-6-11	16.99	--	0.72	5.94	12.27	--
18-6-11	17.65	1.71	0.94	6.09	11.17	--

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE G. CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Midbrain/Thalamus

Animal Number	NE	DA	DOPAC	5-HT	5-HIAA	HVA
14-7-13	29.76*	13.32	3.25	6.62	15.42	1.00
15-7-13	25.65	13.75	3.40	14.05	24.38	4.59
16-7-13	35.48	16.62	3.62	16.00	30.38	--
17-7-13	42.82	16.15	4.00	17.79	40.84	3.30
18-7-13	39.41	19.98	4.19	15.64	35.14	--

*pmole/mg protein

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE H. SUMMARY TABLE OF CATECHOLAMINE AND INDOLEAMINE CONCENTRATIONS IN NORMAL FISCHER 344 RATS

Compound	Hypothalamus	Cerebellum	Pons/ Medulla	Hippocampus	Striatum	Cortex	Midbrain/ Thalamus
NE	114.62* ±1.23 n=5	18.59 ±1.26 n=5	38.53 ±5.52 n=5	26.31 ±2.23 n=5	-- -- --	16.82 ±0.75 n=5	34.62 ±3.12 n=5
DA	29.70 ±6.93 n=5	-- -- --	5.10[b] ±0.17 n=4	3.18 ±0.59 n=2	367.56 ±44.75 n=5	1.61[e] ±0.11 n=2	15.96 ±1.19 n=5
DOPAC	8.13 ±0.28 n=5	0.47 ±0.04 n=5	2.36 ±0.22 n=5	1.09 ±0.30 n=5	98.05 ±9.74 n=5	0.83[f] ±0.05 n=4	3.69 ±0.18 n=5
5-HT	17.20 ±2.19 n=5	0.87[a] ±0.05 n=4	14.59 ±2.43 n=5	9.58[c] ±0.20 n=4	7.39 ±1.22 n=5	6.21[g] ±0.12 n=4	15.87[h] ±0.77 n=4
5-HIAA	30.56 ±1.71 n=5	2.47 ±0.31 n=5	18.93 ±3.57 n=5	22.33 ±3.24 n=5	26.05[d] ±0.91 n=4	10.27 ±1.02 n=5	29.23 ±4.39 n=5
HVA	-- -- --	-- -- --	2.46 ±1.02 n=4	-- -- --	46.84 ±3.30 n=5	-- -- --	2.96 ±1.05 n=3

*Mean ± SEM

[a] Animal No. 15 rejected by Q test at 0.05; Q = 0.866
[b] Animal No. 17 rejected by Q test at 0.05; Q = 0.779
[c] Animal No. 14 rejected by Q test at 0.05; Q = 0.838
[d] Animal No. 14 rejected by Q test at 0.05; Q = 0.726
[e] Animal No. 15 rejected by Q test at 0.05; Q = 0.978
[f] Animal No. 15 rejected by Q test at 0.05; Q = 0.865
[g] Animal No. 14 rejected by Q test at 0.05; Q = 0.844
[h] Animal No. 14 rejected by Q test at 0.05; Q = 0.665

NE - Norepinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE I. CRITICAL VALUE LIST FOR 5 PICOMOLE STANDARD FROM THE INDOLEAMINE METHOD

Standard	Animal No.	Conc. (pmole)	Date	Retention Time	Peak Height	r-correlation	y-intercept	Slope
DOPAC	14	5.0	9-15-87	6.48	974437	0.999931	-24421	199934
	15	5.0	9-16-87	6.33	973043	0.999916	-19087	198240
	16	5.0	9-17-87	6.08	948966	0.998870	-24417	205886
	17	5.0	9-18-87	6.32	959209	0.999659	-28844	203781
	18	5.0	9-21-87	6.54	953760	0.998983	-61544	212245
5-HT	14	5.0	9-15-87	7.17	733076	0.999043	4853	138642
	15	5.0	9-16-87	6.94	723844	0.999221	-13405	140996
	16	5.0	9-17-87	6.62	735968	0.999416	45980	136136
	17	5.0	9-18-87	6.88	765884	0.994206	72440	123272
	18	5.0	9-21-87	7.15	713929	0.999238	9976	134852
5-HIAA	14	5.0	9-15-87	11.26	849949	0.999453	-9728	180601
	15	5.0	9-16-87	10.95	862703	0.999630	-6743	177574
	16	5.0	9-17-87	10.54	922043	0.999949	15010	178406
	17	5.0	9-18-87	10.90	900886	0.999743	28451	176344
	18	5.0	9-21-87	11.42	832642	0.999893	38398	165586
HVA	14	5.0	9-15-87	15.69	334700	0.998062	2540	69103
	15	5.0	9-16-87	15.26	345412	0.969420	124051	50624
	16	5.0	9-17-87	14.68	413675	0.991286	17725	68620
	17	5.0	9-18-87	15.29	306814	0.999902	104	61907
	18	5.0	9-21-87	16.09	410914	0.986596	68787	58874

DOPAC - 3,4-dihydroxyphenylacetic acid
5-HT - 5-hydroxytryptamine
5-HIAA - 5-hydroxyindole acetic acid
HVA - Homovanillic acid

TABLE J. CRITICAL VALUE LIST FOR 20 PICOMOLE INTERNAL STANDARD FROM THE CATECHOLAMINE METHOD

Standard	Animal No.	Conc. (pmole)	Date	Retention Time	Peak Height	r-correlation	y-intercept	Slope
NE	14	20	9-15-87	4.63	678731	0.956857	308232	17033
	15	20	9-15-87	4.62	532734	0.936177	204327	19557
	16	20	9-17-87	4.49	576230	0.953154	304601	18227
	17	20	9-18-87	4.49	604780	0.958438	257740	18898
	18	20	9-21-87	4.58	711134	0.963785	283374	18415
DOPA	14	20	9-15-87	5.73	206957	0.999709	9333	9646
	15	20	9-16-87	5.72	142998	0.985768	-13069	9579
	16	20	9-17-87	5.57	216444	0.999796	6118	10112
	17	20	9-18-87	5.61	185832	0.999185	-31605	11470
	18	20	9-21-87	5.86	302317	0.969109	-472	10369
EPI	14	20	9-15-87	6.47	389180	0.999755	21622	17605
	15	20	9-16-87	6.46	317860	0.997491	-23441	18293
	16	20	9-17-87	6.27	399316	0.999851	13343	19246
	17	20	9-18-87	6.27	381907	0.999929	-6952	19933
	18	20	9-21-87	6.42	466059	0.995415	-2584	19757
DA	14	20	9-15-87	13.47	158846	0.999686	9265	7104
	15	20	9-16-87	13.36	137145	0.999476	-1668	7087
	16	20	9-17-87	12.91	161148	0.999996	3198	7868
	17	20	9-18-87	12.85	148277	0.999424	-9124	7999
	18	20	9-21-87	13.30	142813	0.999913	-10977	7887

NE - Norepinephrine
DOPA - DL-β-3,4-dihydroxyphenylalanine
EPI - Epinephrine
DA - Dopamine

TABLE K. EXTERNAL STANDARD LIST FROM THE CATECHOLAMINE METHOD

Date	Standard	Concentration (pmole)	Retention Time	Peak Height
9-14-87	NE	10	4.62	876586
	DOPA	10	5.86	454800
	EPI	10	6.52	534411
	DA	10	13.78	195208
	DOPAC	10	17.74	198837
	DBA	10	8.46	366284
9-15-87 (morning)	NE	10	4.54	902392
	DOPA	10	5.64	481167
	EPI	10	6.36	556103
	DA	10	13.25	209260
	DOPAC	10	17.06	207493
	DBA	10	8.20	383141
9-15-87 (afternoon)*	NE	10	4.62	889182
	DOPA	10	5.68	442230
	EPI	10	6.44	523376
	DA	10	13.32	171401
	DOPAC	10	17.10	172197
	DBA	10	8.26	360736
9-16-87 (morning)	NE	10	4.64	927467
	DOPA	10	5.78	476850
	EPI	10	6.50	554125
	DA	10	13.50	210011
	DOPAC	10	17.42	207192
	DBA	10	8.36	380902
9-16-87 (afternoon)	NE	10	4.60	847937
	DOPA	10	5.70	388075
	EPI	10	6.42	488915
	DA	10	13.26	139514
	DOPAC	10	17.08	135239
	DBA	10	8.24	346792
9-17-87 (morning)	NE	10	4.63	794707
	DOPA	10	5.75	417918
	EPI	10	6.45	499504
	DA	10	13.33	162946
	DOPAC	10	17.09	155278
	DBA	10	8.27	345960

*Afternoon external standards were run at the end of sample analysis.

NE - Norepinephrine
DOPA - DL-β-3,4-dihydroxyphenylalanine
EPI - Epinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
DBA - 3,4-dihydroxybenzylamine

TABLE K. (Continued)

Date	Standard	Concentration (pmole)	Retention Time	Peak Height
9-17-87 (afternoon)	NE	10	4.47	852142
	DOPA	10	5.49	379610
	EPI	10	6.21	492482
	DA	10	12.71	148676
	DOPAC	10	16.33	122090
	DBA	10	7.93	362652
9-18-87 (morning)	NE	10	4.50	893890
	DOPA	10	5.59	470776
	EPI	10	6.27	558152
	DA	10	12.85	202863
	DOPAC	10	16.61	193917
	DBA	10	8.01	388859
9-18-87 (afternoon)	NE	10	4.50	686651
	DOPA	10	5.58	255009
	EPI	10	6.26	398381
	DA	10	12.82	82868
	DOPAC	10	16.56	51873
	DBA	10	8.00	300183
9-21-87 (morning)	NE	10	4.61	845200
	DOPA	10	5.89	414682
	EPI	10	6.47	500251
	DA	10	13.45	180078
	DOPAC	10	17.47	171546
	DBA	10	8.33	350216
9-21-87 (afternoon)	NE	10	4.58	830043
	DOPA	10	5.84	388671
	EPI	10	6.40	487143
	DA	10	13.24	167422
	DOPAC	10	17.14	151602
	DBA	10	8.22	344247

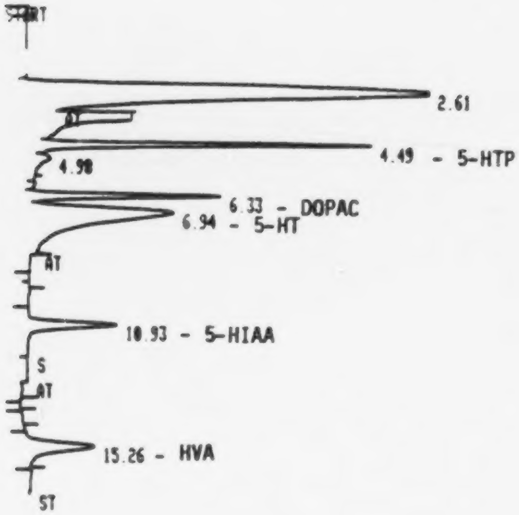
*Afternoon external standards were run at the end of sample analysis.

NE - Norepinephrine
DOPA - DL-β-3,4-dihydroxyphenylalanine
EPI - Epinephrine
DA - Dopamine
DOPAC - 3,4-dihydroxyphenylacetic acid
DBA - 3,4-dihydroxybenzylamine

TABLE L. DBA 50 PICOMOLE INTERNAL STANDARD LIST FROM THE CATECHOLAMINE METHOD

Date	Animal No.	Retention Time	Peak Height	Mean ± SEM
9-15-87	14	8.34	668822	635249 ± 24317
		8.33	673935	
		8.32	629624	
		8.31	568613	
9-16-87	15	8.30	522161	576776 ± 35215
		8.28	510500	
		8.26	647188	
		8.25	627256	
9-17-87	16	8.03	698350	699121 ± 3763
		8.03	708100	
		8.02	689774	
		8.03	700261	
9-18-87	17	8.00	709519	717448 ± 17339
		8.01	679293	
		8.01	717827	
		8.01	763153	
9-21-87	18	8.26	583101	650832 ± 35052
		8.26	650279	
		8.24	622426	
		8.24	747521	

DBA - 3,4-dihydroxybenzylamine



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RUN #   97              SEP/16/87  14:23:35

HEIGHT%
   RT        HEIGHT TYPE    AR/HT     HEIGHT%
   2.61     8575808 ↓SPH    0.599      59.842
   4.49     1844430  SHB    0.268      12.870
   4.98       43183  TBP    0.260       0.301
   6.33      973043  TPV    0.167       6.790
   6.94      723844  TVB    0.619       5.051
  10.93     1825028  SPB    0.264      12.735
  15.26      345412   PB    0.374       2.410

TOTAL HGHT= 1.4331E+07
MUL FACTOR= 1.0000E+00
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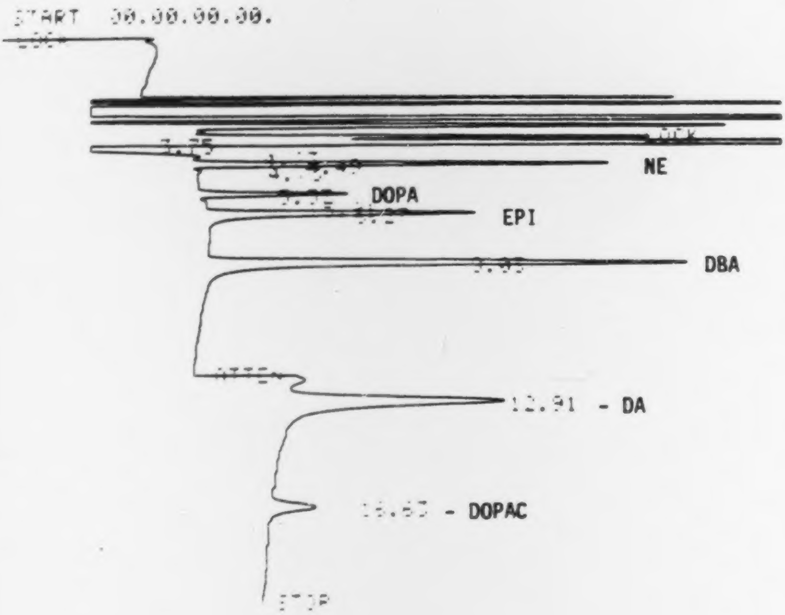
FIGURE 1. The elution profile of a mixture of standards (5 pmole) for the indoleamine method.



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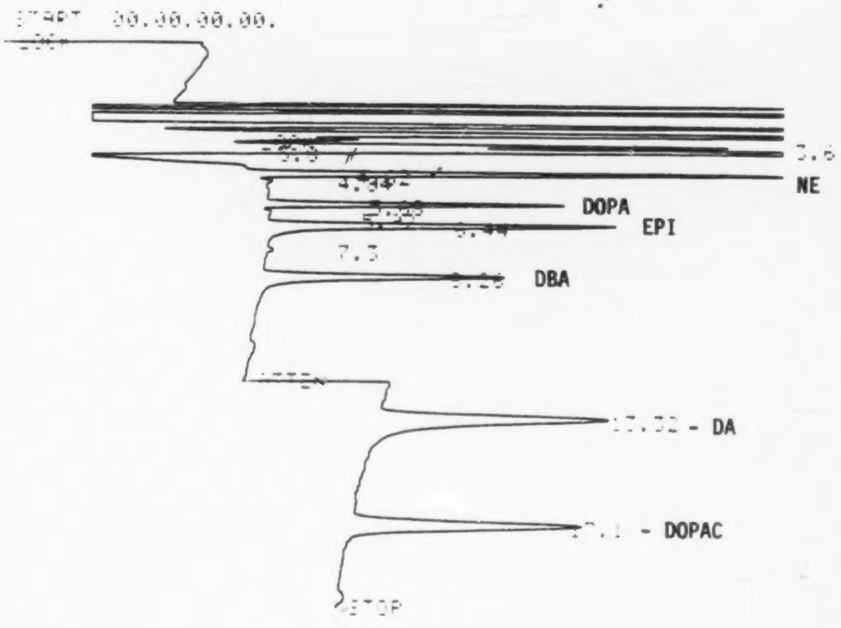
C-R1A
SMPL *        00
FILE *         3
REPT *       128
METHOD      1041

    *    NAME    TIME          CONC      MK        HEIGHT
    0            3.75          38.8387    E       1499645
    0            4.23           3.268              126184
    0            4.49          17.5134    V        676230
    0            4.73           0.7933    V         30631
    0            5.57           5.6056             216444
    0            5.91           0.2376               9174
    0            6.27          10.3417    V        399316
    0            8.03          18.3388             708100
    0           12.91           4.1735             161148
    0           16.63           0.8892              34335
            TOTAL              99.9999            3861210
```

FIGURE 2. The elution profile of a mixture of internal standards (20 pmole) for the catecholamine method.



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C-R3A
SMPL #        00
FILE #         3
REPT #       107
METHOD      1041

   #    NAME   TIME          CONC      MK        HEIGHT
   0            3.6          15.1066              752082
   0            3.8          32.0646   E         1596333
   0            4.62         17.8605   E          889182
   0            4.84          0.961    V           47847
   0            5.68          8.8828              442230
   0            5.92          0.2379               11845
   0            6.44         10.5127   V          523376
   0            7.3           0.226    T           11253
   0            8.26          7.2459              360736
   0           13.32          3.4428              171401
   0           17.1           3.4588              172197
          TOTAL             100.                 4978485
```

FIGURE 3. The elution profile of a mixture of external standards (10 pmole) for the catecholamine method.

DISCUSSION

Although the data in this report represent those of only five animals, changes in mobile phase and assay conditions, refinement of brain dissections and adjusting data reduction parameters required the use of many more animals. Once the protocols were determined and no more alterations made, the tissue from the five animals in this report were prepared and assayed under identical conditions. For each method, DOPAC was eluted. It was decided that the peak from the indoleamine method yielded the most consistent results and was used to quantify DOPAC in the various brain regions. Although DOPA and 5-HTP were separated adequately in the standards, control animals demonstrated very low or nondetectable levels in most brain regions. Using the methods described, we are currently determining the elution profiles of animals that have received i.p. injections of NSD-1015. Once these present methods are approved and modified, if necessary, to comply with GLP requirements, they will be validated with data from additional control animals.

"B"

FDA 224-87-2436
1Y03-ES-7-0159-00

INTERAGENCY AGREEMENT
BETWEEN THE
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES
AND THE
FOOD AND DRUG ADMINISTRATION

The National Institute of Health Sciences (NIEHS) agrees to provide the Food and Drug Administration the services outlined under the terms and conditions as stated herein.

Purpose and Background

One of the primary functions of the Center for Food Safety and Applied Nutrition (CFSAN) of the Food and Drug Administration (FDA) is to assess the toxicity and human health risk following exposure to chemicals in the food supply. These chemicals included the intentionally added food additives, as well as substances present as contaminants from food manufacturing processes or agricultural production. The toxicological testing of food additives and contaminants includes acute and long-term general toxicity, as well as testing for teratogenesis, mutagenesis and carcinogenesis. At the present time there is no systematic testing for neurobehavioral toxicity because until recently the methodology and interpretation of results were not sufficiently developed.

Over the past few years, however, considerable progress has been made in the development of animal testing procedures to evaluate changes in cognitive and other behavioral parameters following experimental manipulations and exposure to drugs and chemicals. Others changes in central nervous system function such as a alteration in seizure threshold can also be evaluated in animal models. These tests can now be applied to the evaluation of food chemicals for behavioral effects, and of particular interest are those materials which have the potential to modulate the availability and/or synthesis of neurotransmitter molecules in the central nervous system. The general postulate is that changes in the concentration of neurotransmitters could affect a number of behavioral functions and the threshold for seizure activity.

In recent years, CFSAN has begun to approve dipetide food additives which following hydrolyses in the gut and absorption, can cause changes in the balance of plasma amino acid levels reflecting the specific components of the peptide. There is an increasing degree of consensus among neurobehavioral toxicologists that amino acid-type substances should be tested for their ability to alter cognitive and other behavioral parameters and to change the threshold for seizure activity. This agreement with the (NIEHS) will evaluate whether specific alterations of dietary amino acids which serve as neurotransmaitter precursors can alter seizure threshold and other brain neurochemical parameters in a number of animal test systems.

1Y03-ES-7-0159-00

I. Description of Work

A. The NIEHS shall:

1. Prepare a detailed Scientific Plan describing how they expect to address the experimental objectives, taking into account full consideration of the complexities of the issues, and how the work will be accomplished. The FDA will review, comment, approve or disapprove the Scientific Plan within 30 days after receipt.

2. Evaluate the changes in CNS excitability and behavior of adult and developing animals exposed acutely or repeatedly to compounds which may alter the endogenous levels of neurotransmitter precursor amino acids. Neurological endpoints will include measures of seizure proneness, particularly with regard to the development of kindled seizures, and sensorimotor reactivity. Where appropriate, comparisons of the effectiveness of systemic (i.p.) versus oral (gavage) dosing with chemical treatments will be made. Depending upon the outcome of these initial experimental results, focused experiments concerning the effects of specific amino acids, such as phenylalanine or aspartic acid, will be conducted.

3. Determine the relationship of any treatment-related effects with experimental variables, such as post-dose interval, route of exposure, feeding conditions (fasting versus ad libitum feeding), nutrient composition of the diet (specifically high protein or high carbohydrate diets), sex, or circadian period at time of treatment and testing.

4. Conduct all phase of the work under the provisions of quality control guidelines established by NIEHS.

5. Unless otherwise required by the experimental design, animals shall be housed in plastic domiciliary cages, maintained under standard laboratory conditions of controlled temperature and humidity and a constant light/dark cycle, and provide food and water ad libitum. The basal diet shall consist of the NIH-31 formulation.

6. Use a sufficient number of animals for each treatment and experimental conditions to produce statistically valid data.

1Y03-ES-7-0159-00

EXPECTED OUTPUTS

A report summarizing the experiments performed evaluating whether compounds which alter the endogenous levels of neutrotransmitter precursor amino acids can cause neurobehavioral changes, including alterations in seizure control in laboratory animals, and whether such changes are influenced by certain experimental variables involving dosing, time of testing and dietary conditions.

B. Reporting Requirements

Within 30 days of the effective date of the Interagency Agreement, the NIEHS shall prepare a detailed Scientific Plan describing how they expect to address the experimental objectives.

The NIEHS shall submit quarterly written progress reports, a final written report, and make oral presentations to the agency as requested by the Project Officers. As a minimum, the quarterly reports will describe progress of the project, the experiments conducted and shall include the raw data obtained from the experiments. A brief description of the next planned quarter's work will be included in each progress report.

II. Name and Address of Participating Federal Agency

Laboratory of Behavioral and Neurological Toxicology
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina 27709

Liaison Officer

Hugh Tilson, Ph.D
J.S. Hong, Ph.D.

Telephone No.: (919) 541-3309 or 541-2358

III. Name of the FDA Participating Unit

Food and Drug Administration
Center for Food Safety and Applied Nutrition
Park Bldg., Room 3-20
5600 Fishers Lane
Rockville, Maryland 20857

Liaison Officers

David G. Hattan, Ph.D.
Chief, Regulatory Affairs Staff (HFF-204)
Office of Nutrition and Food Sciences, CFSAN
Washington, D.C. 20204

Telpehone No.: (202) 245-3117

1Y03-ES-7-0159-00

Thomas J. Sobotka, Ph.D.
Neurobehavioral Toxicology Team, HFF-216
Office of Toxicological Sciences, CFSAN
Washington, D.C. 20204

Telephone No.: (202) 245-1304

IV. Period of Agreement

This agreement, when accepted by both parties, will have an effective period of performance from date of signature through September 30, 1987 and may be modified by mutual consent of both parties or terminated by either party upon a thirty (30) day advance written notice to the other. The anticipated duration of this agreement is two years.

V. Funding

A. An estimated cost of $50,440 for FY-87 is established for FDA to reimburse NIEHS for services provided under this agreement.

B. NIEHS shall submit billings on SF-238 to the FDA Accounting Branch (HFA-120), 5600 Fishers Lane, Rockville, MD 20857. Billing not to exceed $50,440 will be chargeable to FDA Appropriation No. 7570600, CAN 7-6991295-F-436, PMS 22340W-10, O.C. 25.31.

C. Administrative billing requirements shall be in accordance with GAO Policy and Procedure, Title 7, Section 8.4.

VI. Authority

The Economy Act as amended June 30, 1932, 15 USC 1535 (formerly 31 USC 686).

APPROVED AND ACCEPTED FOR THE
NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES

By: Charles E Leasure Jr

Title: Executive Officer, NIEHS

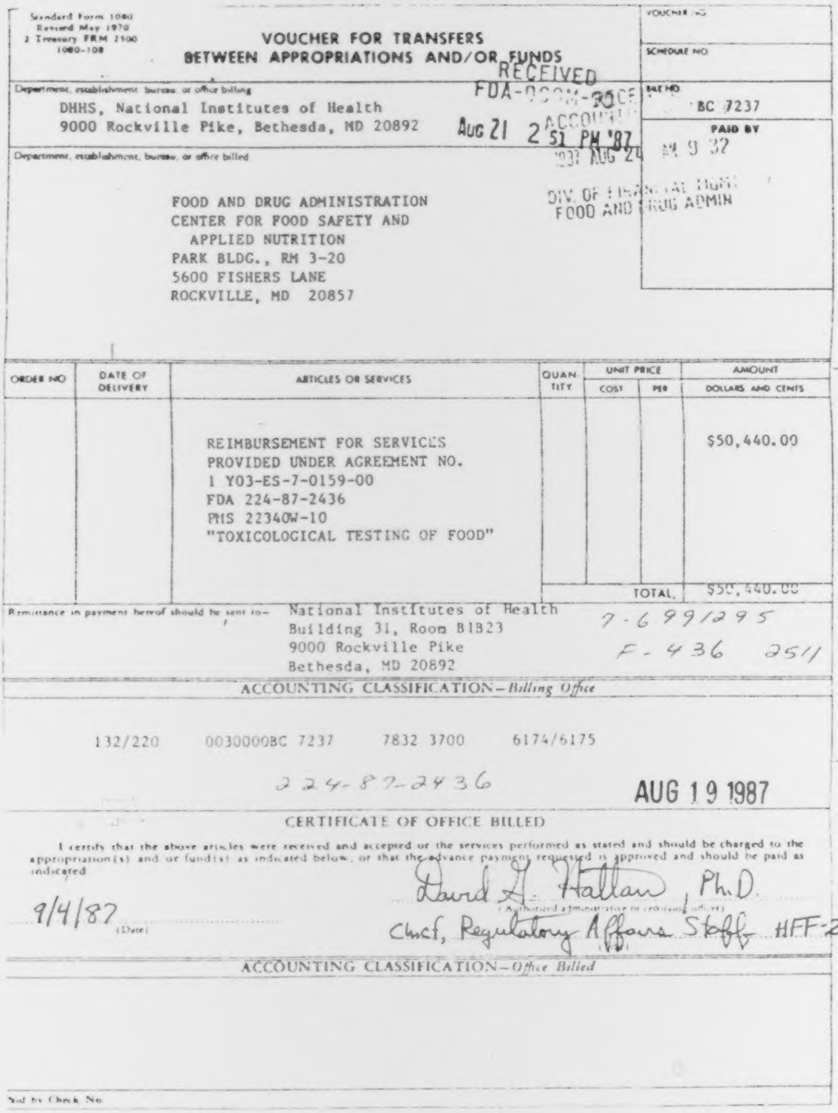
Date: May 8, 1987
SW EX 2

APPROVED AND ACCEPTED FOR THE
FOOD AND DRUG ADMINISTRATION

By:
James L. Tidmore

Title: Director, Division of Contracts and Grants Management, OMO

Date: Jun 8, 1987



Standard Form 1080
Revised May 1970
2 Treasury FRM 2500
1080-108

VOUCHER FOR TRANSFERS BETWEEN APPROPRIATIONS AND/OR FUNDS

VOUCHER NO	
SCHEDULE NO	
BILL NO	BC 7237
PAID BY	

Department, establishment, bureau, or office billing

DHHS, National Institutes of Health
9000 Rockville Pike, Bethesda, MD 20892

RECEIVED
FDA-OCOM-90CF
AUG 21 2 51 PM '87

ACCOUNTING
1987 AUG 24 AM 9 32
DIV. OF FINANCIAL MGMT
FOOD AND DRUG ADMIN

Department, establishment, bureau, or office billed

FOOD AND DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY AND
APPLIED NUTRITION
PARK BLDG., RM 3-20
5600 FISHERS LANE
ROCKVILLE, MD 20857

ORDER NO	DATE OF DELIVERY	ARTICLES OR SERVICES	QUANTITY	UNIT PRICE		AMOUNT
				COST	PER	DOLLARS AND CENTS
		REIMBURSEMENT FOR SERVICES PROVIDED UNDER AGREEMENT NO. 1 Y03-ES-7-0159-00 FDA 224-87-2436 PHS 22340W-10 "TOXICOLOGICAL TESTING OF FOOD"				$50,440.00
					TOTAL	$50,440.00

Remittance in payment hereof should be sent to—

National Institutes of Health
Building 31, Room B1B23
9000 Rockville Pike
Bethesda, MD 20892

7-6991295
F-436 2511

ACCOUNTING CLASSIFICATION—*Billing Office*

132/220 0030000BC 7237 7832 3700 6174/6175

224-87-2436

AUG 19 1987

CERTIFICATE OF OFFICE BILLED

I certify that the above articles were received and accepted or the services performed as stated and should be charged to the appropriation(s) and/or fund(s) as indicated below, or that the advance payment requested is approved and should be paid as indicated.

9/4/87
(Date)

David G. Hattan, Ph.D.
(Authorized administrative or certifying officer)

Chief, Regulatory Affairs Staff HFF-204
(Title)

ACCOUNTING CLASSIFICATION—*Office Billed*

Paid by Check No

"C"

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date · October 21, 1987

From Project Officer

Subject Memorandum of Need: Request to Establish a New Interagency Agreement

To Ms. Olia Hopkins
Chief, State Contracts and Assistance Agreements Branch (HFA-520)

1. Interagency Agreement

   This is a new Interagency Agreement entitled: Effects of Aspartame and Related Compounds on Human Performance; No. 224-88-2435

2. Purpose of Agreement

   The Food and Drug Administration (FDA), Center for Food Safety and Applied Nutrition, will reimburse the Federal Aviation Administration (FAA) for providing necessary program support and services to FDA as described in the Attachment.

3. Description of Support and Services

   The FDA shall receive program support and services from FAA as described in Section III of the Attachment.

4. Participating Agencies and Liaison Officers

Federal Aviation Administration

Jerry Hordinsky, M.D.
Federal Aviation Administration Aeronautics Center
Civil Aeronautics Medical Institute
AAM-110
P.O. Box 25082
Oklahoma City, OK 73125

(405) 686-4807

Food and Drug Administration

John C. Wallingford, Ph.D.
Center for Food Safety and Applied Nutrition
Clinical Nutrition Branch
Food and Drug Administration
200 C Street SW
Washington, DC 20204

(202) 485-0084

5. Period of Agreement

From the date of signature for approximately two (2) years, (until September 30, 1989).

6. Funding

FDA Appropriation Data:

Fiscal year 1988
Appropriation Number: 7580600 25.31
Allotment Number: 8-6991295-F-435
PMS Number: 223142/10

7. Estimated Costs

FY 1988

For each research center accepting (to include subject reimbursement, professional time computer time, supplies, recruitment costs and travel)	$16,400
Indirect costs (at 30% of direct costs)	$ 4,920
Per accepting site	$21,320
expected number of accepting sites	3
Total FY 1988 costs	$63,960

FY 1989

For each research center accepting (as enumerated for FY 1988)	$13,050
Indirect costs (at 30% of direct costs)	$ 3,915
Per accepting site	$16,965
expected number of accepting sites	2
Total site costs	$33,930
Final report preparation	$ 1,500
Total FY 1989 costs	$35,430
Total project costs	$99,390

8. Method of Payment

The FAA shall submit invoices on Standard Form 1081 for "support and services" to:

Food and Drug Administration
Accounting Branch (HFA-120)
5600 Fishers Lane
Rockville, MD 20857

SIGNATURE PAGE

PROJECT TITLE: Effects of Aspartame and Related Compounds on Human Performance

IDENTIFICATION #: 224-88-2435

FUNDING DATA: See attached HHS-393

John C Wallingford
Project Officer

John N.
Program Manager

Approved:
Director, Office of Nutrition and
Food Sciences
10-21-87
Date

Approved: Denise Knox Riley
Actg. Financial Management Officer
10-22-87
Date

Approved:
Actg. Director, Office of Management
10/22/87
Date

Approved:
AL Director, Center for Food Safety
and Applied Nutrition
10/22/87
Date

Approved:
for Director, Division of Financial
Management
10/22/87
Date

Approved: for
Associate Commissioner for
Regulatory Affairs
10-22-87
Date

FDA 224-88-2435

INTERAGENCY AGREEMENT
BETWEEN THE
FEDERAL AVIATION ADMINISTRATION
AND THE
FOOD AND DRUG ADMINISTRATION

I. INTRODUCTION

The Federal Aviation Administration (FAA) agrees to furnish to the Food and Drug Administration (FDA) the support and services described under section III, Statement of Work. This inter- agency agreement allows the agencies to meet their respective objectives in the area of cognitive behavioral effects from use of substances ingested as food additives or drugs.

Aspartame has been tested extensively for safety. It is currently being tested in animals to further define any effects on central nervous system functions such as seizure thresholds and regional brain transmitter amino acids. These types of effects are difficult to relate directly to human behavior at the levels of aspartame typically consumed. The FDA, in response to continued public concern about possible neurological and cognitive behavioral effects of aspartame ingestion, is interested in assessing the behavioral effects of aspartame in humans directly.

Cognitive tests are of particular interest to FDA (considering post-market surveillance complaints of neurobehavioral effects of aspartame ingestion) and FAA (since the tests measure very subtle aspects of performance). Testing for cognitive effects under controlled and standardized conditions should provide a sensitive assay for possible central nervous system (CNS) activity by aspartame.

Currently, the FAA has contracted three independent research centers to assess the cognitive performance of certified pilots in accordance with American Medical Association recommendations. The core tests are similar among the centers and are commonly used in cognitive testing. For example, one center's tests derive from the unified tri-service cognitive performance assessment battery (UTC-PAB). This battery consists of 25 tests measuring various components of cognition; some of the tests have demonstrated sensitivity and reliability to detect impairment in cognitive function due to environmental stressors (e.g., sleep loss) and commonly consumed substances (e.g., caffeine, ethanol). For test validation, comparisons are being made with results from individuals with diagnosed organic brain dysfunction, e.g., seizures, head trauma, CNS infections.

The FAA is interested directly in the results of tests with aspartame, as it is consumed frequently and in large amounts by FAA personnel. Additionally, the positive control substances selected for validation of the tests in these studies are of interest to the FAA independent of the tests with aspartame.

The population of certified pilots is particularly valuable as subjects for the tests required by FDA, since

1) they engage routinely in complex cognitive tasks; positive effects of the test substances are unlikely to be due to learning curve acquisition of skills, and the variance in an individual's inter-test performance is likely to be small, maximizing test sensitivity to agent effects, and

2) the results of the baseline tests will allow a comparison to results of subsequent studies of effects on psychomotor skills (using flight simulators).

II. TITLE:

Effects of Aspartame and Related Compounds on Human Performance

III. STATEMENT OF WORK:

The FAA shall offer on an equal basis to each of its contractors # DTFA 0287C87068, DTFA 0287C87069 and DTFA 0287C87070, Cognitive Function Evaluation in Medical Certification of Airmen, the opportunity to append to their contracts studies on the cognitive performance effects of aspartame ingestion. The FAA, via accepting contractors, shall:

(1) Append to existing contracts, a scientific plan(s) developed by the phase 'A' contractor(s), in cooperation with the FDA, for study of cognitive performance effects of aspartame ingestion. The plan(s) shall describe the experimental objectives, the potential problems and limitations to carrying out the research, the contingent plans to overcome the problems and limitations, detailed protocols and consent forms. The plan(s) shall be forwarded by the FAA to the FDA for final approval.

(2) During the first year, determine in a selected set of standardized human subjects, acting as their own controls, the effects of ingestion of a bolus at or below the Acceptable Daily Intake (50 mg/kg) of aspartame on outcomes of tests measuring complex cognitive functions. The tests employed shall derive from the UTC-PAB or comparable tests and represent a broad range of cognitive function. The aspartame treatment outcomes shall be compared to no treatment or vehicle only (intrasubject reproducibility), or ingestion of phenylalanine, or suitable physiological substances (e.g., caffeine or ethanol) yielding behavioral consequences (positive controls).

(3) Subsequently test (depending on initial test outcomes) at least one of the following:
a) alternate outcomes (e.g., EEG, serum amino acids),
b) dose-response, or chronic ingestion effects,
c) effects of co-ingestion of selected dietary components (e.g., a high carbohydrate meal), or nutrients (e.g., tyrosine or tryptophan) or
d) a second set of subjects of either greater potential risk of adverse effects (PKU heterozygotes) or a group of normal controls representing the general population.

The FDA shall:

(1) Assist the contractors in the development of the experimental protocols.

(2) Submit the experiment protocols and consent forms to the FDA Research Involving Human Subjects Committee for review and approval. (N.B. Aspartame is not known to have any toxicological effects in non-phenylketonuric humans at the doses to be tested, although it is possible that a small number of individuals have increased sensitivity at these doses.)

The FAA and FDA shall jointly:

(1) Ascertain that neither the studies under the existing contracts nor the studies described in this statement of work shall interfere with or compromise the validity of the other.

(2) Decide on the area(s) for additional study as listed under section III (3) above, depending on results of the initial studies, and on remaining funds available.

IV. REPORTING REQUIREMENTS:

The scientific plan will be submitted to the FAA and FDA within 60 days of the effective date of the Interagency Agreement. FAA will receive and forward to FDA, quarterly, written progress reports from each participating contractorto include original data obtained and description of problems encountered during the previous quarter, and a summary of the progress expected during the following quarter.

The FAA shall receive and forward to the FDA a final written report from each accepting contractor evaluating the effects of aspartame on cognitive performance, with consideration to the dosage used, limitations of the tests used, other experimental variables investigated, and characteristics of the specific population(s) studied. The report shall be written in a format suitable for publication in a peer reviewed scientific journal.

The FAA or its contractors shall present the results at a seminar to the FDA at the completion of the studies, at a time agreed upon by all participating parties.

V. PARTICIPATING FEDERAL AGENCIES AND LIAISON OFFICERS:

Food And Drug Administration

John C. Wallingford, Ph.D.
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 'C' Street, SW
Washington, DC 20204

(202) 485-0084

Federal Aviation Administration

Jerry Hordinsky, M.D.
Federal Aviation Administration Aeronautics Center
Civil Aeronautics Medical Institute
AAM-110
PO Box 25082
Oklahoma City, OK 73125

(405) 686-4807

VI. FUNDING:

The FDA shall reimburse FAA an estimated total of $100,000 (approximately $64,000 during FY 1988 and $35,000 during FY 1989) for the support and services specified in the Statement of Work above.

VII. METHOD OF PAYMENT:

A. The FAA shall submit invoices on Standard Form 1081 for "support and services rendered" to:

Food and Drug Administration
Accounting Branch (HFA-120)
5600 Fishers Lane
Rockville, MD 20857

B. All agreed-to costs shall be charged to the following accounting and appropriation data:

Fiscal year 1988

Appropriation #:	7580600 25.31
Allotment Number:	8-6991295-F-435
PMS Number:	223142/10

C. Administrative billing requirements shall be in accordance with GAO Policy and Procedure, Title 7, Section 8.4.

VIII. PERIOD OF AGREEMENT:

The terms of this agreement shall be effective for two years from the date of signature, subject to extension mutually agreed to by the parties. Modification of the agreement shall be by mutual consent of both parties. If either party desires to terminate this agreement, a written notice to the other party shall be sent and received thirty (30) days in advance of the desired termination date.

IX. AUTHORITY:

This agreement is entered into under the authority of the Economy Act approved June 30, 1932, as amended 31 U.S.C. 1535.

ACCEPTED AND APPROVED FOR THE FOOD AND DRUG ADMINISTRATION	ACCEPTED AND APPROVED FOR THE FEDERAL AVIATION ADMINISTRATION
Name: ____________________	Name: ____________________
Title: ____________________	Title: ____________________
Date: ____________________	Date: ____________________

References

Committee on military nutrition research, Food and Nutrition Board, (1986) Cognitive Testing Methodology. National Academy Press, Washington, DC.

Perez, WA, Masline, PJ, Ramsey, EG and Urban, KE (1987) Unified tri-services cognitive performance assessment battery: Review and methodology. National Technical Information Service, Springfield, VA.

Hegge, FW (ed)(1986) Joint working group on drug dependent degradation in military performance, Proceedings of in-process review, prepared under contract by Metters Industries, Inc. Silver Spring, MD.

International Aspartame Workshop Proceedings (1986) International Life Sciences Institute/Nutrition Foundation, Washington, DC.

Krause, W, Halminski, M, McDonald, L, Dembure, P, Salvo, R, Freides, D and Elsas, L (1985) Biochemical and neuropsychological effects of elevated plasma phenylalanine in patients with treated phenylketonuria. J. Clin. Invest. 75:40-48.

Bradstock, MK, Seruda, MK, Marks, JS, Barnard, RJ, Crane, NT, Remington, PL and Trowbridge, FL (1986) Evaluation of reactions to food additives: the aspartame experience. Am. J. Clin. Nutr. 43:464-469.

O'Donoghue, JL (ed)(1983) Neurotoxicity of industrial and commercial chemicals. Vol. 1, CRC Press, Inc., Boca Raton, FL.

July 8 (1983) Food additives permitted for direct addition to food for human consumption- Aspartame. Federal Register 48:31376.

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DEPARTMENT OF
HEALTH AND HUMAN SERVICES
PURCHASE/SERVICE/STOCK REQUISITION

REQUISITION NUMBER 98092

OFFICE CODE/SYMBOL

BPA and Call No. ______

TO
State Assistance and Agreements Br.HFA-520

REQUEST FOR
☐ PURCHASE ☒ SERVICE ☐ STOCK ISSUE ☐ RENTAL/LEASE

REQUESTING ORGANIZATION
Food and Drug Administration

CUSTODIAL AREA
CFSAN

DATE
10/21/87

OBJECT CLASS
25.31

FOR REFERENCE CALL
Robert G. Coon

EXTENSION
245-1098

APPROPRIATION
7580600 223142/10

DELIVER TO
John C. Wallingford
Division of Nutriton, CFSAN, FDA,
200 C Street SW
Washington, DC 20204

CAN
8-6991295-F-435

[redacted] est. amount
$ 63,960

ITEM NO.	DESCRIPTION (INCLUDE STOCK NUMBER, MODEL/PART NO., ETC.)	QUANTITY REQUIRED	UNIT OF ISSUE	COST UNIT	COST TOTAL
	MEMORANDUM OF NEED - NEW INTERAGENCY AGREEMENT				
	IAG. NO. 224-88-2435				
	IAG TITLE: Effects of Aspartame and Related Compounds on Human Performance				
	Period of Funding and Amount Available for Obligation:	12 Months			$ 63,960
	Estimate amount for FY 89: $ 35,430				
	Distribution of HHS 393: HFA-520 (orig pink) HFY-1 (blue) HFA-120 (yellow) HFF-20 (pink) HFA-100 (yellow) Hff-9 (white)				
	Director, Div. of Financial Management Date				

I certify that the property/services requested are required for Government business, and are not available from excess or current assets.*

FUNDS AVAILABLE (Signature/Title)
Denise Knox Riley
D.K.Riley, Acting Chief, FMB

DATE 10/22/87

TOTAL $ 63,960

REQUESTED BY (Signature/Title)*
Robert G. Coon (for)
Wallingford, Project Officer

DATE 10/22/87

RECEIVING OFFICIAL - I certify that the quantities indicated in the "Quantity Required" column above have been received in total or as annotated.

RECOMMEND APPROVAL (Signature/Title)*

DATE

RECEIVING OFFICIAL (Signature/Title)

DATE

APPROVED BY (Signature/Title)*
Denise Knox Riley
D.K.Riley, Acting Chief, FMB

DATE 10/22/87

ORDER NO. (PO, DO, FEDSTRIP, ETC.)

ORDER DATE

PROPERTY MANAGEMENT OFFICER (Signature)*

DATE

VOUCHER NO.

VOUCHER DATE

Commissioner YOUNG. To me, one of the most interesting ones is a study we are negotiating now with FAA for $96,390. This project is entitled "Effects of Aspartame and Related Compounds on Human Performance," and studies will be undertaken on the effects of ingestion of aspartame by volunteer humans on performance tests of cognitive functions. In this case, FAA has a very large battery of tests that they use on volunteers each year, and they are cognitive tests. We feel that human studies will be most helpful here, and I did talk with the FAA yesterday; it is now up to the point of their review by General Counsel, and we hope that this will be instituted soon, because I would like to see the effect on human beings in cognitive studies. Although we can speculate on chemistry, the real bottom line is what is the effect on behavior of human beings, and we are trying to focus on that.

In my testimony I have also outlined for you the variety of issues that will be looked at as we focus on what the significance of blood phenylalanine levels are. I will not take time away from this, but I would call your attention to the fact that normal levels of phenylalanine are about 3 to 5 micromoles per deciliter, and when we had a large dose of aspartame, 34 milligrams per kilogram, that is approximately 10 times higher than the actual intake, that phenylalanine raised from 3 to 5 to 10 to 11 micromoles per deciliter.

I have also studied amino acid transport in bacteria as part of my early work, looking at d-alanine, l-alanine, dicycloserine, and others, and I know full well the type of studies that you are going to be exposed to on transport of amino acids and their effect on serotonin synthesis and dopamine synthesis.

The real issue, though, is can you measure cells precisely—we are dealing with our brain in an enclosed skull, so we are primarily focusing on whole-brain studies, homogenates, and other actions—and, can we link this to cognitive changes. That is exactly what our studies are designed to deal with.

If one looked at, as I said, the 34 milligrams per kilogram intakes, which raised slightly the amounts of blood phenylalanine, one would have to consume 10 cans of diet beverage in a single sitting to reach these increased blood levels. And I tried to give in my testimony a wide variety of examples of this, and I do not want to take your time by going through that.

I would just like to quote my conclusion. We do not have any medical or scientific evidence that undermines our confidence in the safety of aspartame. This confidence is based on years of study, years of analysis of adverse reactions, which I presented for you, and research in the scientific community, including studies supported by FDA. Additionally I have assembled for you a summary of the world literature that has been inventoried since 1981, and I will submit this for the record as well so that you can have that.

[Information supplied for the record follows:]

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: Inventory of aspartame world literature since 1981.

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SER:
rt

ROG:


N  - 22839-47-0
N  - 7421-84-3 (CAS)
N  - 53906-69-7 (CAS)
N  - 53906-69-7 (TOXLIT) (TOXLIT65)
1  - L-Phenylalanine, N-L-alpha-aspartyl-, 1-methyl ester (9CI)
0  - TOXLINE
0  - TOXLIT
0  - TOXLIT65
0  - RTECS
0  - TSCAINV
0  - MEDLINE
0  - MED83
0  - MED80
0  - MED77
0  - CANCERLIT
0  - HSDB

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ROG:
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ROG:


U  - Stegink LD
U  - Filer LJ Jr
U  - Baker GL
I  - Effect of aspartame and sucrose loading in glutamate-susceptible
     subjects.
O  - Am J Clin Nutr; VOL 34, ISS 9, 1981, P1899-905


U  - Ishii H
U  - Koshimizu T
U  - Usami S
U  - Fujimoto T
I  - Toxicity of aspartame and its diketopiperazine for Wistar rats by
     dietary administration for 104 weeks.
O  - Toxicology; VOL 21, ISS 2, 1981, P91-4


U  - Lines DR
I  - Aspartame doses for phenylketonuria [letter]
O  - J Nutr; VOL 111, ISS 9, 1981, P1688-90


J  - Stegink LD
J  - Koch R
J  - Blaskovics ME
J  - Filer LJ Jr
J  - Baker GL
U  - McDonnell JE
I  - Plasma phenylalanine levels in phenylketonuric heterozygous and
     normal adults administered aspartame at 34 mg/kg body weight.
O  - Toxicology; VOL 20, ISS 1, 1981, P81-90


U  - Dickson D
I  - Aspartame sugar substitute: new court overruled [news]
O  - Nature; VOL 292, ISS 5821, 1981, P283
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U - Ishii H
I - Incidence of brain tumors in rats fed aspartame.
O - Toxicol Lett; VOL 7, ISS 6, 1981, P433-7

U - Stegink LD
U - Filer LJ Jr
U - Baker GL
I - Plasma and erythrocyte concentrations of free amino acids in
adult humans administered abuse doses of aspartame.
O - J Toxicol Environ Health; VOL 7, ISS 2, 1981, P291-305

U - Stegink LD
U - Brummel MC
U - McMartin K
U - Martin-Amat G
U - Filer LJ Jr
U - Baker GL
U - Tephly TR
I - Blood methanol concentrations in normal adult subjects
administered abuse doses of aspartame.
O - J Toxicol Environ Health; VOL 7, ISS 2, 1981, P281-90

U - Shaw JH
I - Sweeteners--an overview. Part. 1.
O - Dent Abstr; VOL 26, ISS 3, 1981, P116-20 (REF: 17)

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U - SINCLAIR S, ED.
I - ASPARTAME: NEWEST SWEETENER ON THE MARKET. ITS INTRODUCTION
FOLLOWS MORE THAN 10 YEARS OF TESTING.
O - ORAL HEALTH 1981, 71(10) 33-34

1
U - LINE_ [illegible]
U - STEGINK LD
U - FILER LF JR
U - BAKER GL
U - MCDONNELL [illegible]
I - ASPARTAME DOSES FOR PHENYLKETONURIA: LETTERS.
O - J. NUTR. 1981, 111(9) 1688-1690

2
U - ISHII H
U - KOSHIMIZU T
U - USAMI S
U - FUJIMOTO T
I - TOXICITY OF ASPARTAME AND ITS DIKETOPIPERAZINE FOR WISTAR RATS BY
DIETARY ADMINISTRATION FOR 104 WEEKS.
O - TOXICOLOGY 1981, 21(2) 91-94

U - Ikeda T
I - Sugar substitutes: reasons and indications for their use.
I - TOXBIB/82/188916
O - Int Dent J; VOL 32, ISS 1, 1982, P33-43 (REF: 43)

U - Stegink LD
U - Filer LJ Jr
U - Baker GL
I - Effect of aspartame plus monosodium L-glutamate ingestion on
plasma and erythrocyte amino acid levels in normal adult subjects
fed a high protein meal.
I - TOXBIB/83/071642
O - Am J Clin Nutr; VOL 36, ISS 6, 1982, P1145-52

I - Aspartame and other sweeteners.
I - TOXBIB/83/002788
O - Conn Med; VOL 46, ISS 7, 1982, P411

U - EPIDEMIOLOGY AND CLINICAL TOXICOLOGY UNIT, FOOD AND DRUG
ADMINISTRATION
I - ASPARTAME: SUBJECT LISTING
I - EPIDEM/099015
O - SCIENTIFIC LITERATURE COVERAGE LISTING, UNPUBLISHED 1982, 1 P.

U - URIBE M
I - POTENTIAL TOXICITY OF A NEW SUGAR SUBSTITUTE IN PATIENTS WITH
LIVER DISEASE: LETTER.
I - EPIDEM/005704
O - N. ENGL. J. MED. 1982, 306(3) 173-174

U - PORIKOS KP
U - HESSER MF
U - VAN ITALLIE TB
I - CALORIC REGULATION IN NORMAL-WEIGHT MEN MAINTAINED ON A PALATABLE
DIET OF CONVENTIONAL FOODS.
I - EPIDEM/001165
O - PHYSIOL. BEHAV. 1982, 29(2) 293-300

ROG:

U - Yellowlees H
I - Aspartame [letter]
I - TOXBIB/84/001155
O - Br Med J [Clin Res]; VOL 287, ISS 6396, 1983, P912-3

U - Beardsley T
I - Sour welcome for aspartame [news]
I - TOXBIB/83/297716
O - Nature; VOL 305, ISS 5931, 1983, P175

- Stegink LD
- Filer LJ Jr
- Baker GL
- Plasma amino acid concentrations in normal adults fed meals with added monosodium L-glutamate and aspartame.

I - TOXBIB/83/293645
O - J Nutr; VOL 113, ISS 9, 1983, P1851-60

U - Wurtman RJ
I - Neurochemical changes following high-dose aspartame with dietary carbohydrates [letter]
I - TOXBIB/83/271332
O - N Engl J Med; VOL 309, ISS 7, 1983, P429-30

U - Stegink LD
U - Brummel MC
U - Filer LJ Jr
U - Baker GL
I - Blood methanol concentrations in one-year-old infants administered graded doses of aspartame.
I - TOXBIB/83/267838
O - J Nutr; VOL 113, ISS 8, 1983, P1600-6

U - Filer LJ Jr
U - Baker GL
U - Stegink LD
I - Effect of aspartame loading on plasma and erythrocyte free amino acid concentrations in one-year-old infants.
I - TOXBIB/83/267837
O - J Nutr; VOL 113, ISS 8, 1983, P1591-9

U - Horwitz DL
U - Bauer-Nehrling JK
I - Can aspartame meet our expectations?
I - TOXBIB/83/266622
O - J Am Diet Assoc; VOL 83, ISS 2, 1983, P142-6 (REF: 36)

U - Sbravati C
U - Fischer RG
I - Pediatric drug information. What sugar substitutes are available and are there any differences between them?
I - TOXBIB/83/168528
O - Pediatr Nurs; VOL 9, ISS 2, 1983, P138

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U  - NOVITCH M
I  - ASPARTAME AS AN INACTIVE INGREDIENT IN HUMAN DRUG PRODUCTS:
     LABELING REQUIREMENTS.
I  - EPIDEM/008764
O  - FED. REG. 1983, 48(237) 54993-54995

U  - NOVITCH M
I  - FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN
     CONSUMPTION:  ASPARTAME.
I  - EPIDEM/008762
O  - FED. REG. 1983, 48(132) 31376-31382


   - FERNSTROM JD
   - FERNSTROM MH
   - GILLIS MA
   - ACUTE EFFECTS OF ASPARTAME ON LARGE NEUTRAL AMINO ACIDS AND
     MONOAMINES IN RAT BRAIN.
I  - EPIDEM/001096
O  - LIFE SCI. 1983, 32(14) 1651-1658

     ADMINISTERED GRADED DOSES OF ASPARTAME.
I  - EPIDEM/[illegible]
O  - J. NUTR. 1983, 113(8):1600-1606

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U  - ANONYMOUS
I  - ASPARTAME CRITICS PERSIST, RECOMMEND AVOIDANCE DURING PREGNANCY
O  - MED WORLD NEWS; 25(4):23-26,1984


U  - Sadler MJ
I  - Recent aspartame studies.
O  - Food Chem Toxicol; VOL 22, ISS 9, 1984, P771-3


U  - Olney JW
I  - Excitotoxic food additives--relevance of animal studies to human
     safety.
O  - Neurobehav Toxicol Teratol; VOL 6, ISS 6, 1984, P455-62 (REF: 49)
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U - Waggoner WF
I - Aspartame--a review.
O - Pediatr Dent; VOL 6, ISS 3, 1984, P153-8

U - Hagiwara A
U - Fukushima S
U - Kitaori M
U - Shibata M
U - Ito N
I - Effects of three sweeteners on rat urinary bladder carcinogenesis initiated by N-butyl-N-(4-hydroxybutyl)-nitrosamine.
O - Gann; VOL 75, ISS 9, 1984, P763-8

I - Evaluation of consumer complaints related to aspartame use.
O - MMWR; VOL 33, ISS 43, 1984, P605-7

U - Grasso P
U - Conan J
U - Fce F
I - Aspartame: succession of false alarms.
O - Hum Toxicol; VOL 3, ISS 4, 1984, P257-9

U - Franz M
I - Is aspartame safe?
O - Diabetes Educ; VOL 10, ISS 2, 1984, P56-7

U - Yokogoshi H
U - Roberts CH
U - Caballero B
U - Wurtman RJ
I - Effects of aspartame and glucose administration on brain and plasma levels of large neutral amino acids and brain 5-hydroxyindoles.
O - Am J Clin Nutr; VOL 40, ISS 1, 1984, P1-7

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U - Burgert SL
I - Aspartame--a new low-calorie sweetener.
O - Iowa Med; VOL 74, ISS 5, 1984, P215-7

1
U - Shahangian S
U - Ash KO
U - Rollins DE
I - Aspartame not a source of formate toxicity [letter]
O - Clin Chem; VOL 30, ISS 7, 1984, P1264-5

4
U - NOVITCH M
I - FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION; ASPARTAME.
O - FED. REGIST. 1984, 49(36) 6672-6682

U - REYNOLDS WA
U - PARSONS L
U - STEGINK LD
I - NEUROPATHOLOGY STUDIES FOLLOWING ASPARTAME INGESTION BY INFANT
NONHUMAN PRIMATES
O - FOOD SCI. TECHNOL. 1984, 12() 363-378

6
U - GOSSEL TA
I - A REVIEW OF ASPARTAME: CHARACTERISTICS, SAFETY AND USES
O - U.S. PHARM. 1984, 9(26) 28-30

2
U - Babbitt D
I - Artificial sweetener observations [letter]
O - Pediatr Nurs; VOL 10, ISS 1, 1984, P84

3
U - Wenz E
I - Aspartame and PKU [letter]
O - J Am Diet Assoc; VOL 84, ISS 1, 1984, P101

U - MAHALIK MP
U - GAUTIERI RF
I - REFLEX RESPONSIVENESS OF CF-1 MOUSE NEONATES FOLLOWING MATERNAL
ASPARTAME EXPOSURE
O - RES COMMUN PSYCHOL PSYCHIAT BEHAV; 9:385-403,1985

U - Gaull GE
I - Aspartame and seizures [letter]
O - Lancet; VOL 2, ISS 8469-70, 1985, P1431

U - Sturtevant F
I - Does aspartame cause methanol toxicity? [letter]
O - Food Chem Toxicol; VOL 23, ISS 10, 1985, P961

U - Wurtman RJ
I - Aspartame: possible effect on seizure susceptibility [letter]
O - Lancet; VOL 2, ISS 8463, 1985, P1060

U - Nehrling JK
U - Kobe P
U - McLane MP
U - Olson RE
- Kamath S
U - Horwitz DL
I - Aspartame use by persons with diabetes.
O - Diabetes Care; VOL 8, ISS 5, 1985, P415-7

U - Sturtevant FM
I - Use of aspartame in pregnancy.
O - Int J Fertil; VOL 30, ISS 1, 1985, P85-7 (REF: 20)

I - Aspartame. Review of safety issues. Council on Scientific
Affairs.
O - JAMA; VOL 254, ISS 3, 1985, P400-2

U - Shader RI
U - Greenblatt DJ
I - Phenelzine and the dream machine--ramblings and reflections
[editorial]
O - J Clin Psychopharmacol; VOL 5, ISS 2, 1985, P65

0
U - Wolraich M
U - Milich R
U - Stumbo P
U - Schultz F
I - Effects of sucrose ingestion on the behavior of hyperactive boys.
O - J Pediatr; VOL 106, ISS 4, 1985, P675-82

1
U - G:uttler F
U - Lou H
I - Aspartame may imperil dietary control of phenylketonuria [letter]
O - Lancet; VOL 1, ISS 8427, 1985, P525-6

2
U - Briggs TA
I - How sweet is it?
O - Dent Abstr; VOL 30, ISS 2, 1985, P76-8

3
U - Ferguson JM
I - Interaction of aspartame and carbohydrates in an
eating-disordered patient [letter]
O - Am J Psychiatry; VOL 142, ISS 2, 1985, P271

4
U - Novick NL
I - Aspartame-induced granulomatous panniculitis.
O - Ann Intern Med; VOL 102, ISS 2, 1985, P206-7

U - KULCZYCKI A JR
I - ASPARTAME-INDUCED URTICARIA
O - ASPARTAME-INDUCED URTICARIA. UNPUBLISHED MATERIAL, 1985.
KULCZYCKI TO HATTAN, 850419. 5 P.

7
U - ROTHSCHILD L JR, ED
I - FOOD CHEMICAL NEWS.
O - FOOD CHEM. NEWS 1985, 27(43) 1-99

U - Simon RA
I - Adverse reactions to food additives.
O - New Engl Reg Allergy Proc; VOL 7, ISS 6, 1986, P533-42 (REF: 55)

U - Maher TJ
I - Neurotoxicology of food additives.
O - Neurotoxicology; VOL 7, ISS 2, 1986, P183-96 (REF: 42)

U - Pardridge WM
I - The safety of aspartame [letter]
O - JAMA; VOL 256, ISS 19, 1986, P2678

U - Gaull GE
I - Clinical and behavioral effects of aspartame [letter]
O - Toxicol Appl Pharmacol; VOL 85, ISS 3, 1986, P478-9

U - Moser RH
I - Panic attacks and aspartame [letter]
O - Lancet; VOL 2, ISS 8510, 1986, P808

U - Caballero B
U - Mahon BE
U - Rohr FJ
U - Levy HL
U - Wurtman RJ
I - Plasma amino acid levels after single-dose aspartame consumption
in phenylketonuria, mild hyperphenylalaninemia, and heterozygous
state for phenylketonuria.
O - J Pediatr; VOL 109, ISS 4, 1986, P663-71

U - Franz M
I - Is it safe to consume aspartame during pregnancy? A review.
Nutrition update.
O - Diabetes Educ; VOL 12, ISS 2, 1986, P145-7

U - Bickel H
U - Trefz FK
I - [Aspartame: a sweetening agent with a high phenylalanine content]
O - Monatsschr Kinderheilkd; VOL 134, ISS 7, 1986, P478-80

U - Drake ME
I - Panic attacks and excessive aspartame ingestion [letter]
O - Lancet; VOL 2, ISS 8507, 1986, P631

O
U - Johns DR
I - Migraine provoked by aspartame [letter]
O - N Engl J Med; VOL 315, ISS 7, 1986, P456

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1
U  - Kruesi MJ
U  - Rapoport JL
I  - Diet and human behavior: how much do they affect each other?
O  - Annu Rev Nutr; VOL 6, 1986, P113-30 (REF: 94)

2
U  - Walton RG
I  - Seizure and mania after high intake of aspartame.
O  - Psychosomatics; VOL 27, ISS 3, 1986, P218, 220

3
U  - Bradstock MK
J  - Serdula MK
   - Marks JS
   - Barnard RJ
   - Crane NT
   - Remington PL
   - Trowbridge FL
   - Evaluation of reactions to food additives: the aspartame
     experience.
O  - Am J Clin Nutr; VOL 43, ISS 3, 1986, P464-9

4
U  - Coulombe RA Jr
U  - Sharma RP
I  - Neurobiochemical alterations induced by the artificial sweetener
     aspartame (NutraSweet).
O  - Toxicol Appl Pharmacol; VOL 83, ISS 1, 1986, P79-85


5
J  - Kulczycki A Jr
[  - Aspartame-induced urticaria.
]  - Ann Intern Med; VOL 104, ISS 2, 1986, P207-8
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U - Alfin-Slater RB
U - Pi-Sunyer FX
I - Sugar and sugar substitutes. Comparisons and indications.
O - Postgrad Med; VOL 82, ISS 2, 1987, P46-50, 53-6

I - More pointers on PKU [letter]
O - MCN; VOL 12, ISS 4, 1987, P239

U - Stegink LD
I - The aspartame story: a model for the clinical testing of a food additive.
O - Am J Clin Nutr; VOL 46, ISS 1 Suppl, 1987, P204-15 (REF: 74)

I - The safety of aspartame [letter]
O - JAMA; VOL 258, ISS 2, 1987, P205-6

U - Zametkin AJ
U - Karoum F
U - Rapoport JL
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Commissioner YOUNG. I am particularly interested in two of the studies that you will hear about from investigators today—the study of Dr. Matalon, (we look forward to evaluating his work which was presented in a recent conference); and the study of Dr. Elsas, from Emory, who looked at PKU carriers. He reported a change in brain waves, technically, a depression of the mean power frequency, as well as changes in cognitive performance. And we will study these as the data are available to us.

In addition to studying the world literature, we will be looking at studies supported by FDA.

We would have expected to see significant, serious, reproducible adverse reactions, in view of the tens of millions in our population who consume aspartame, if there was a direct link between one particular syndrome and aspartame per se. A significant number of adverse reactions have not been reported, however, despite the enormous publicity.

There have been clearly documented a few allergic reactions—one of urticaria that was very nicely done on challenge, and another on panniculitis. Both of these were seen, and clearly, we would expect with any food additive a set of reactions; and I have pulled, and I will introduce for the record, an analysis of a British report that essentially says the Commission of the European Communities, on the basis of existing evidence, assigned a prevalence of 0.03 percent to 0.15 percent for food additive intolerance.

[Information supplied follows:]

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: "Food Intolerance and Food Aversion, A joint report of the Royal College of Physicians and the British Nutrition Foundation." Journal of the Royal College of Physicians of London 18(2):3-41 (April 1984). [See page 5 of the report].

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EMBARGOED for

18th April 1984

EMBARGOED for
18th April 1984

Food Intolerance and Food Aversion

A JOINT REPORT OF THE ROYAL COLLEGE OF PHYSICIANS AND THE BRITISH NUTRITION FOUNDATION

Membership of the Joint Committee

Chairman
Professor M. H. Lessof, Professor of Medicine, Guy's Hospital Medical School, London

Secretary
Dr J. R. Gray, Consultant Nutritionist and formerly Science Director, British Nutrition Foundation

Members
Professor R. Hoffenberg, President, Royal College of Physicians
Sir Douglas Black, Emeritus Professor of Medicine, Manchester University, and past President, Royal College of Physicians
Dr M. Brook, Director of Research, Beecham Products, Middlesex
Miss M. A. Conry, District Dietitian, The General Infirmary at Leeds
Professor J. Edelman, Director of Research, The Lord Rank Research Centre, Buckinghamshire
Dr A. Ferguson, Reader in Medicine and Hon. Consultant Gastroenterologist, Western General Hospital, Edinburgh
Dr R. Finn, Consultant Physician, Royal Liverpool Hospital
Dr J. Hubert Lacey, Senior Lecturer and Hon. Consultant Psychiatrist, St George's Hospital, London
Dr J. V. Leonard, Senior Lecturer, Institute of Child Health, University of London
Dr D. H. Shrimpton, Director-General, British Nutrition Foundation
Dr J. O. Warner, Consultant Paediatrician, The Brompton Hospital, London

Observers
Dr B. MacGibbon, Senior Principal Medical Officer, DHSS, London
Dr G. Pincherle, Senior Medical Officer, DHSS, London

Mr G. M. G. Tibbs, Secretary, Royal College of Physicians
Miss E. Bernfeld
Miss A. Overton } Committee Secretaries

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PREFACE

The concept of allergy to food has attracted a great deal of attention in recent years. Although this condition has not always been very clearly defined, wide publicity is given to the unproven claim that food allergy is becoming more common, that (despite evidence to the contrary) food processing exacerbates the problem, and that the medical profession is not sufficiently well informed to deal with it. It is, however, becoming clear that, if allergy is taken to imply a specific immune reaction of the body, allergic reactions are present only in a minority of cases in which there is an unpleasant reaction to a food. Food intolerance may occur when food contains components which are either generally toxic or toxic to certain individuals, or when the nature of the reaction is as yet unknown. Diagnosis is, however, difficult because it depends on attempts to reproduce a clinical response in a patient who, at different times, may develop symptoms rapidly or more slowly and after smaller or larger quantities of the same food. There is also great uncertainty about the prevalence of this condition in the community at large and particularly about the importance of psychological factors which may lead to food aversion. For these reasons a survey of the present state of knowledge is indicated.

Against this background, the Royal College of Physicians and the British Nutrition Foundation formed a committee to consider these various areas of concern and to make whatever recommendations might be necessary. The terms of reference of the Joint Committee were:

1. To define food intolerance.
2. To assess the frequency of clinical reactions to fresh or stored food preparations.
3. To consider the biological and psychological mechanisms involved in food intolerance, as they affect the public at large and as they affect susceptible groups of individuals who suffer from allergic disorders, enzyme defects, or the effects of other metabolic disorders or drug treatment.
4. To assess the implications of food intolerance for the medical profession, the food industry, the government and the public and to make recommendations for these groups concerning the possible need for further educational, preventive, investigative, therapeutic or research endeavours in this area.

The report of the Joint Committee is presented in the following pages. The Appendix discusses sources of information on food products, and a Glossary has been added in case readers are unfamiliar with some of the terms used.

1. INTRODUCTION

1.1 Definitions

When the body's immune defence mechanism shows an exaggerated response to harmless grains of grass pollen or to articles of food, there can be unpleasant symptoms of 'allergy' without any obvious benefit to the person concerned. Thus, food allergy may be a cause of symptoms but needs to be distinguished from other clinical conditions which are related to food. Two main conditions have been identified, food intolerance and food aversion (Table 1). The following definitions should be used:

Food intolerance itself, which is a reproducible, unpleasant (i.e. adverse) reaction to a specific food or food ingredient and is not psychologically based. This occurs even when the affected person cannot identify the type of food which has been given (for example, when it is disguised by flavouring and given as a purée).

Table 1. Food aversion and intolerance

Food aversion	Food intolerance
Psychological food intolerance	Enzyme defects
Food avoidance	Pharmacological
	Irritant and toxic
	Allergic
	Fermentation of food residues
	Other

Food allergy, which is a form of food intolerance in which there is also evidence of an abnormal immunological reaction to the food.

Food aversion, which comprises both psychological avoidance—when the subject avoids food for psychological reasons—and psychological intolerance, which is an unpleasant bodily reaction caused by emotions associated with the food rather than the food itself and which does not occur when the food is given in an unrecognisable form.

In those who have reproducible adverse reactions to food due to causes other than food aversion or allergy, various mechanisms may be responsible. These mechanisms include:

(a) A lack of particular enzymes; for example, in people who do not tolerate cow's milk because they cannot digest lactose (alactasia).

(b) A pharmacological effect; for example, due to large amounts of caffeine in strong coffee or tea.

(c) An as yet unexplained histamine-releasing effect in unsensitised individuals; for example, caused by the consumption of foods such as shellfish, strawberries, and pawpaw.

(d) An irritant effect on the mucous membranes of the mouth or bowel, especially when the mucosa is diseased, for example, irritation caused by highly spiced curry or very hot coffee.

(e) An indirect effect caused by the effects of fermentation of unabsorbed food residues in the lower bowel
(f) Mechanisms as yet unidentified.

1.2 Prevalence of Food Intolerance

A precise assessment of the prevalence of food intolerance is difficult, since diagnosis has depended largely on subjective methods associated with clinical screening tests and the interpretation of a patient's previous history. Thus, widely varying estimates of prevalence may be found in the literature. It is suggested that between 0.3 per cent and 20 per cent of children suffer from, or have suffered from, symptoms caused by some form of dietary intolerance[1]. The wide range of incidence reflects the effects of selective bias and different diagnostic criteria employed in various studies and emphasises the difficulty in establishing a useful estimate of prevalence.

Conditions such as 'cow's milk protein intolerance', the most common food allergy in young children, have been estimated to have a prevalence between 0.2 per cent and 7.5 per cent[2]. In a similar survey involving 400 infants monitored from birth to two years of age, the * incidence of milk intolerance was 0.5 per cent[3].

When it comes to assessing the frequency of allergy or intolerance to food additives, the problem is considerably more difficult. This is because a number of colours and additives are often used in combination and appear in a wide variety of foodstuffs. As any one individual may react in a similar way to structurally related colours and additives, it may be difficult to identify which particular food or food component triggers the adverse reaction. Studies concerning reactivity to food additives have therefore been somewhat restricted to selected populations and, in the main, to patients attending hospital for the treatment of 'allergy-like' diseases.

To obtain an approximate figure for the prevalence of additive-induced adverse reactions in the skin, Juhlin[4] reviewed the literature for relevant information and, also using his own data, reached the following conclusions: (a) In patients with chronic urticaria, 33–50 per cent of individuals tested reacted to one or more food additives. (b) Tartrazine produced a reaction in 5–46 per cent of those tested, other azo dyes gave positive reactions in 5–20 per cent of those tested. (c) Among the preservatives tested, benzoate derivatives produced reactions in 3–44 per cent of individuals and the antioxidants, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA), were implicated in reactions in 14–15 per cent of individuals. Thus, even in sensitive individuals, there was a very wide range of reactivity to different additives.

These studies cannot provide true estimates of prevalence in the whole population, since an extrapolation from responses obtained in a selected group is based on the assumption that there is no difference in susceptibility among the population at large, which is unlikely to be the case. It is reasonable to assume that the susceptibility of the general population to adverse reactions to additives is likely to be considerably less than that of the special groups studied.

It has been estimated that in every 10 million people about 40,000 will show intolerance to aspirin (0.4 per cent), 6,000 to tartrazine (0.06 per cent) and 5,000 to benzoates (0.05 per cent)[4]. In France, sensitivity to tartrazine was estimated to be between 0.03 per cent[5] and 0.15 per cent[6]. A recent study in Denmark[7] employed a more systematic approach. Initially, the frequency of asthma, chronic rhinitis and chronic urticaria was assessed in the general population over 16 years of age and determined to be in the order of 3.8 per cent, 1.9 per cent and 0.5 per cent respectively. The frequency of adverse reactions to food additives within each group was then determined by reference to previous case histories and previous provocation tests. It was concluded that 0.01–0.1 per cent of the population were sensitive to both tartrazine and benzoates. These figures are in the same order as those suggested by Juhlin[4]. The Commission of the European Communities[8], on the basis of existing evidence, assigned a prevalence of 0.03 per cent to 0.15 per cent for food additive intolerance. When one considers that almost everyone in the population has probably been exposed to tartrazine at some time or another, sensitisation to tartrazine is low.

1.3 Genetic Factors

It would appear that genetic factors can predispose individuals to a number of diseases and this may also hold true for certain types of food intolerance, including those caused by enzyme defects (see Chapter 5.1). It is well established that allergic disorders are more common in the children of atopic parents[9]. The mode of inheritance of susceptibility to allergy is not known but there are suggestive links between the HLA haplotype A1/B8 and atopic eczema[10] and between HLA B8/W3 and gluten sensitivity[11]. Indeed, recent experimental evidence suggests that there may well exist a whole class of non-HLA linked genes that also control immune responses to foreign substances[12]. Genetic factors are of importance in relation to the many types of food intolerance and may be relevant to atopic disease and IgE production. Various types of inherited immune deficiency can also predispose to atopic disease, including deficiencies of complement (C2) or of immunoglobulin A, and defects of T cells or of the mechanisms that stimulate the phagocytic function of leukocytes[13].

Genetic factors may only come into play following the appropriate exposure to the environmental stimulus. Developmental and/or environmental pressures would then be superimposed upon a genetic predisposition before a state of intolerance could appear. A predisposition to dietary intolerance is obviously a real phenomenon, but we remain unclear as to how this operates.

1.4 The Clinical Patterns

Where the affected person develops an immediate swelling of the lips, tingling of the mouth or throat, vomiting or abdominal pain, it may not be difficult to establish the link between a food and the reaction which follows. Even late complications such as diarrhoea, constipation, bloating of the abdomen and fatty stool may be suggestive of

* * * * *

Commissioner YOUNG. I am one of the individuals who has a natural intolerance. I am allergic to crab, and I do watch very carefully, because I will not only have respiratory distress, but tachycardia, and could go into cardiovascular shock. It is not unlikely for people to have allergic reactions to foods, and we did find some of those here.

Despite our failure to find a significant number of adverse reactions that point to a single syndrome at this time, we shall remain vigilant and not be complacent in our analysis of research; we will continue to conduct research, and we will continue to review consumer complaints.

In addition, the agency will remain in close contact with those who are skeptical of aspartame's safety. For example, the Center has met with Dr. Richard Wurtman of MIT to discuss a number of his hypotheses about aspartame. The Center has also met with the Aspartame Consumer Safety Network to discuss issues relating to the safety of aspartame, including the status of pending petitions for approval of new uses for aspartame, the results of our sponsored research, and improving the exchange of aspartame-related data. We have been pleased to receive their comments regarding the operation of the Center's adverse reaction monitoring system. In addition, the Center's scientists have presented data on the operation of the adverse reaction monitoring system and on the reports of aspartame reactions to a variety of scientific meetings and to numerous consumer and industrial groups.

Therefore, based on the evidence to date, the agency has concluded that aspartame, both in the pre- and post-marketing stages, has withstood the requirement of the law that there be reasonable certainty of no harm.

I would be delighted to answer further questions, and I thank you for the opportunity of being able to present results from charts, to try to distinguish between the no-effect, acceptable dietary daily intakes, and the actual intake, which I found most confusing as I started this.

I have also put in my appendix for your consideration the study of the post-market surveillance and actual uses, so that you can compare those during the course of the history of this hearing with what we have found.

Thank you very much, Mr. Chairman. I would be delighted to answer any questions that you have.

[The prepared statement of Commissioner Young and additional material referred to above follow:]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT BY

FRANK E. YOUNG, M.D., PhD.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

NOVEMBER 3, 1987

FOR RELEASE ONLY UPON DELIVERY

Mr. Chairman:

I am here today to provide information about the artificial sweetener aspartame, commonly known as NutraSweet. As you know, aspartame was first marketed in 1981 as a dry, free-flowing sugar substitute for table use and for other uses, such as the sweetening of breakfast cereals, gelatins, puddings and fillings and in dry beverage bases. Subsequent uses we have approved include carbonated beverages in 1983 and a number of other less significant uses. As summarized in Appendix 1, several petitions for additional uses are currently pending before us.

BACKGROUND

Aspartame is a simple compound made up of three components, all of which are normally present in the foods we eat every day. Most food and color additives are not made up of normal physiological components like aspartame is, and only rarely are drugs of natural origin derived from foods safe for human consumption. Thus, the safety considerations of the compound would focus on the quantitative levels consumed, not the qualitative nature of the compound. This distinction is extremely important as we analyze the issues before us today. Furthermore, because aspartame consists only of naturally occurring building blocks of food, it is in contrast to many other food or color additives and new drugs, most of which are new chemical entities not found in nature.

The safety of aspartame is accepted throughout most of thw world. Today, tens of millions of our population consume significant amounts of aspartame-containing products every day. Such is the case in over 60 other countries as well, including most of Western Europe, Japan and recently The Peoples Republic of China and the USSR.

The Bureau of Foods and its successor, the Center for Food Safety and Applied Nutrition (the Center) devoted years of analysis to the evaluation of aspartame. I have been presented with evidence by the Center that documents this process. More recently, a General Accounting Office audit concluded that FDA followed appropriate legal and administrative procedures and requirements in initially approving aspartame for use in dry foods and in subsequently approving additional uses.

Additionally, to provide an extra layer of safety, I requested that postmarket surveillance be initiated for food ingredients of potential health significance as part of the FDA Action Plan, Phase I and II. Aspartame has been included in this program. Furthermore, we have initiated our own research studies, two of which are responsive to specific concerns that you, Mr. Chairman, have expressed about aspartame. Titles and abstracts provided in Appendix 2.

We are aware, of course, that some have raised questions concerning potential health effects of aspartame. While we remain satisfied that our approval of aspartame is appropriate, we also must remain open-minded and receptive to any new data which might affect our views. To this end, we will continue to operate our adverse reaction reporting system for aspartame and other food additives and components, review the results of research performed by others, and will initiate our own studies to augment the knowledge obtained from the first two sources as appropriate. My testimony will focus on three issues: the analysis of adverse reactions; how much aspartame can be safely consumed and the review of research since the initial approval of aspartame.

ANALYSIS OF ADVERSE REACTION REPORTS

The reports of adverse reactions to aspartame present certain difficulties for the epidemiologist because most of them cannot be easily linked to a specific cause. Our first investigation of complaints from all sources was made soon after aspartame consumption increased in 1983 due to its approval for use in soft drinks. The complaints were mild and were common in the general population, such as headache, dizziness, changes in mood, and abdominal discomfort. No specific constellation of symptoms could be identified with the consumption of aspartame.

Since then, FDA has designed and implemented a mechanism to evaluate all consumer complaints concerning food components, including additives such as aspartame. This system, called the Adverse Reaction Monitoring

System (ARMS), catalogues and, in selected cases, investigates complaints sent directly to the FDA or referred to it by the manufacturer, physicians, scientists such as Dr. Richard Wurtman, and others. The NutraSweet Co., which submits for about 40 percent of all complaints received by the FDA, routinely forwards them to us on a monthly basis.

A health professional reviews each of the reports, assesses the severity of the alleged reaction, and designates certain demographic and diagnostic data to be entered into a computer database. For that very small number of cases where serious conditions are reported, we seek additional information on the relationship between product use and symptoms, existing diseases, and drug use. In addition, we specifically attempt to obtain any related medical records or physicians' opinions. In each such case in which our request for medical records and additional information has been honored, the Center has been unable to make a causal connection to aspartame (with the exception of two cases of urticaria, or hives, and another case of a different type of mild skin reaction).

FDA Staff also evaluates all the information in the system on a quarterly basis to determine whether there is new evidence that aspartame ingestion may be causally related to the reactions reported. As of October 23, 1987, the ARMS has evaluated 3,511 of the 3,679 aspartame consumer complaints received by FDA. There still is no consistent pattern of symptoms reported that can be attributed to the use of aspartame. The symptoms reported may occur shortly after ingestion or after prolonged use, and after very small or large intakes. Estimates of complainants' intake are typically well below the ADI.

We have further found that the overall character of reactions with respect to demographic variables, severity, strength of association with aspartame intake, associated product types, and symptoms has remained essentially unchanged over time. Moreover, because the reports are most frequently anecdotal in nature, it is not possible, without other data such as medical records, to eliminate factors other than aspartame consumption as possible causes of the reported effects.

It is worth noting that recent inquiries of health officials in Canada and the United Kingdom indicate that the rate of receipt in those countries of complaints alleged to be associated with aspartame consumption remains minimal and well below the U.S. incidence.

HOW MUCH IS SAFE?

In light of accounts of individuals who feel they might have experienced some harm as a result of using aspartame, questions continue to be raised about how much aspartame it is safe to ingest. As I have already stated, aspartame is made up of basic building blocks of food--phenylalanine, aspartic acid and methanol--that are consumed commonly in much larger amounts from natural sources. Thus, adverse reactions to aspartame in normal, basically healthy people are not something that we would expect to occur.

It is true, of course, that any food or component of food--even water--can have adverse effects if consumed to excess over long periods of time. Additionally, people can develop allergies to foods. For aspartame, therefore, as for any food additive, considerable premarket studies were conducted to learn what effects it might cause at extreme levels of consumption and what those extreme levels would have to be over the long run in order for an effect to occur.

Lifetime feeding studies in laboratory animals revealed a "no effect" level for aspartame that extends upward into a consumption range for humans that is hard to imagine. Specifically, no effect at all was seen at 2000 mg/kg of body weight per day over the lifetimes of the test animals. This amount is equivalent to the aspartame contained in 4.5 twelve-ounce cans of soft drink for every pound of body weight. For the average 60 kg (132 pounds) adult, this translates into 600 cans of soft drink per day.

A threshold effect was seen in the test animals at 4000 mg/kg. At this extreme level, this effect involved a physiological "overload" that took the form of some growth deficits.

After determining a no effect level, a much lower level, known as the "acceptable daily intake" (ADI), is calculated to compare against estimates of what the daily intake of the food additive could be at a highest possible level of actual use. If these estimates of daily intake (EDI), exceed the ADI, the food additive, or a new use for an already marketed food additive, will not be approved.

Why establish an ADI which is way below the no effect level? The reasons for doing so are twofold. First, an ADI establishes a very substantial cushion between actual usage in humans and the no effect level seen in animals, since the effects seen in animals might not translate precisely to human experience. Second, an ADI takes into account the fact that people will not all experience an adverse effect at the same dosage level. As a matter of regulatory prudence, differences in human sensitivity also require the establishment of a substantial cushion between the no effect level and actual usage.

In developing an ADI, a ten-fold margin of safety is traditionally assigned to each of these two potential areas of variation. Thus, when an ADI is based solely on animal data, a safety factor of ten (representing possible differences between reactions in animals data and reactions in humans) is multiplied by a second safety factor of ten that takes into account the range of human sensitivity. The resulting 100-fold safety factor is then divided into the no effect level to provide the ADI.

In cases where human clinical data exists, however, the ten-fold safety factor for animal data might not be necessary. Under such circumstances, an ADI might only need to utilize the ten-fold safety factor that relates to the range of human sensitivity. A ten-fold safety factor still provides a substantial cushion between actual intake and the no effect level.

In the case of aspartame, human clinical data do in fact exist. As a consequence, it was determined that a full 100-fold safety factor was not necessary and that a 40-fold factor could be established. When divided into the no effect level of 2000 mg/kg, this 40-fold safety factor for aspartame provides an ADI of 50 mg/kg.

The ADI is defined as an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk. It focuses on continued exposure over a lifetime and not on the exposure that could occur on any given day.

As I have stated, FDA uses the ADI by comparing it to premarket consumption estimates and postmarket surveys of actual consumption. Different EDIs can be calculated that reflect various assumptions concerning uses of an additive, uses by various age groups or uses by other subgroups of the national population. In the premarketing evaluation of petitions for use of food additives, EDIs for the maximum probable consumer ingestion of the additive are computed.

After marketing approval is granted, FDA monitors actual usage of additives by means of surveys of the domestic food industry for comparison with the premarket EDIs and the ADI. We have been monitoring aspartame usage since 1981, when a specific Postmarketing Survey was instituted as a condition for permitting food additive use. The Survey has two parts: (1) a Poundage Survey, in which the amounts of aspartame sold to different sectors of the food and pharmaceutical industries are reported, and (2) a Dietary Survey, in which the actual ingestion of aspartame-containing foods is reported for a sample population. The results of each survey are reported on a quarterly basis to the Center.

The Poundage Survey shows that the total amount of aspartame added to food rose rapidly in 1982 through 1984, but has reached a plateau since 1985. About three-quarters of the total sold goes into carbonated beverages.

The sample population for the Dietary Survey is a demographically balanced representation of 2,000 households (5,300 individuals) that is chosen and maintained by a private marketing research firm, Market Research Corporation of America. The daily aspartame intakes are statistically distributed into groups according to (1) age ranges, (2) types of aspartame uses, (3) single-day and long-term (14-day average) intakes and, (4) special population groups such as diabetics, persons on weight-reduction diets and women of child-bearing age. We have been receiving quarterly reports of aspartame intake for this sample population since the second quarter of 1984. After a few erratic quarters in which the sample population showed wide swings in aspartame usage, aspartame intakes have become rather predictable. This indicates that the consumer market for aspartame-containing foods has matured. As expected, there continue to be modest seasonal fluctuations. This information is presented in Appendix 3.

Presently, the actual intakes as reflected in the Survey data are about one-half of our premarket estimates. The ratio of one-half applies uniformly across all age groups and across all degrees of use of aspartame foods, (i.e., average and high-frequency consumers). This is not unusual. We consider premarket estimates of intake as an upper limit to actual intake. In computing this premarket EDI, we deliberately err on the side of conservatism by assuming that, if a person eats a type of product that could either contain sugars or aspartame, the product always contains aspartame. Obviously, in real life this assumption is far from correct, and produces an overestimate.

In the most recent survey, the average actual aspartame intake for the entire sample population of aspartame eaters was about 50 mg per person per day. Assuming that the average person weighs 60 kg, this figure is less than 1 mg/kg body weight and less than 2 percent of the ADI. High-frequency users of aspartame-containing foods were found to ingest about 130 mg per person per day, which is 2 mg/kg body weight and only four percent of the ADI.

Young children, of course, have higher rates of aspartame consumption per unit of body weight than adults. For the 2-to-5-year age group, the average intake is 3 percent of the ADI and high frequency intake is between 4 and 16 percent of the ADI. We see considerable seasonal variation in the high frequency ingestion of aspartame by children.

The special population groups of diabetics, weight reducers and women of child bearing age have greater percentages of aspartame consumers than the total sample population. That is, 60 percent of diabetics, 50 percent of weight reducers, and 40 percent of women of child bearing age use aspartame in comparison to 35 percent of the total sample population. However, the amounts of aspartame ingested per day are not too different from the general population. High-frequency diabetic aspartame eaters ingest only 7 percent of the ADI and high frequency weight reducers ingest only 4 percent of the ADI.

FDA scientists have evaluated the data on actual aspartame intakes to determine if there could be a possibility that consumers might exceed the ADI. We have evaluated long-term aspartame intakes for all of the age groups and special populations. The highest aspartame intake for the high-frequency individual in any group of any quarterly report was only 16 percent of the ADI. Hence, the difference in amount between chronic ingestion of aspartame and the ADI continues to be large.

While it is possible to devise a dietary scenario in which an individual eats 50 mg/kg of aspartame, it would not really be feasible for that individual to do so. Such a scenario simply would not be reflective of the way people eat--not even children who love sweets. Too many other foods and nutrients are needed on a daily basis to make such a diet possible.

COMPONENTS AND DECOMPOSITION PRODUCTS

Questions have also been raised by some people about the safety of aspartame's components. Phenylalanine, which makes up about one-half of the aspartame molecule, is one of the 21 amino acids are generally present in proteins. It is consumed in comparatively large quantities (5000 mg) by the average adult each day in a normal, aspartame-free diet. This quantity translates into roughly 83 mg of phenylalanine per kg of body weight for a 60 kg adult. By comparison, the average daily intake of phenylalanine from aspartame is only 1 to 2 mg/kg of body weight per day for all age groups and 2 mg/kg of body weight per day for children 2 to 5 years old. For these children, the average consumption of phenylalanine from protein is 180 mg/kg of body weight per day.

Even though phenylalanine intake from aspartame is typically only a very small fraction of its intake from other sources, the health effects of phenylalanine in aspartame remain a source of concern to some people. Much of this concern focuses on the small segment of the population who suffer from the genetic disorder known as phenylketonuria, or PKU. These people are deficient in the enzyme that metabolizes phenylalanine (phenylalanine hydrolase) and therefore must consume a carefully controlled diet that limits their intake of this particular amino acid. For the benefit of these people, we require that a notice appear on all labeling of food containing aspartame advising of the presence of phenylalanine.

A different situation is presented by individuals who do not themselves suffer from PKU but are, unknowingly, carriers of this genetic defect. Concerns have been raised about the possible risk to them as well as the potential risk to unborn children posed by the consumption of aspartame by pregnant women who are carriers of PKU. While the blood phenylalanine levels from aspartame for PKU carriers do tend to be somewhat higher than for non-carriers on the same diet, the differences are modest and without health significance. One study worth mentioning examined the effect of consuming a single, 34 mg/kg dose of aspartame on both PKU carriers and normal individuals. This amount is the equivalent of drinking 10 cans of soda all at once. The study found that for each type of individual, the phenylalanine level in the blood rose to approximately the same level that it would attain as a result of eating a protein-rich, aspartame-free meal. Moreover, we know from studies that at intakes of aspartame significantly exceeding the ADI, increases in phenylalanine in the blood of PKU carriers are well below the levels known to be associated with neurological deficits in patients with PKU itself.

For the unborn child of a pregnant PKU carrier, the American Academy of Pediatrics has concluded that at typical consumption levels, the increased intake of phenylalanine derived from aspartame does not seem to be sufficiently high to warrant concern. And, as we have seen, pregnant PKU carriers will, in all likelihood, be consuming protein from natural sources that contain phenylalanine in amounts vastly exceeding the quantity that they could reasonably be expected to be consuming through aspartame.

A seven-year study now under way by the National Institutes of Health should provide additional useful information in this area. It is a prospective, multicenter study to determine the influence of diet on levels of phenylalanine in the blood and how this might relate to children born of PKU mothers.

Questions also have been raised about one of aspartame's decomposition products, methanol, regarding how much methanol is consumed during aspartame use and whether the levels may be expected to cause adverse effects in humans. Methanol is both a component of common foods (e.g., there are amounts in orange juice comparable to that derived from aspartame sweetened beverages), and a normal component of the body's metabolism. Nonetheless, methanol can be toxic at high doses.

From estimates based on plasma levels in methanol poisonings, visual and central system toxicities are produced when a methanol dose reaches 200 to 500 mg/kg body weight. For the methanol dose to reach this toxic range from consuming aspartame, an individual would have to rapidly consume 2000-5000 mg/kg of body weight--an obviously impossible event.

Even when a massive "abuse" dose of aspartame is administered in an unusually rapid manner as in a single oral dose, the plasma levels of formate, the toxic metabolite of methanol, are not raised above typical base line levels. In a 1986 study performed with human subjects who received 500 mg aspartame (6-8.7 mg/kg body weight) as a single dose, for example, elevation of blood methanol was quite modest, the peak methanol levels being within the range of concentrations found normally in the tested individuals during control periods without aspartame. Clearly, there is a vast margin between the levels of methanol intake derived from abuse levels of aspartame consumption and methanol intakes associated with ocular or central nervous system toxicity.

REVIEW OF RESEARCH

Many of the areas I have been discussing have been the subject of considerable scientific inquiry. Although FDA does not require the petitioner of an approved food additive to provide safety studies after the additive has been approved unless questions of safety arise, FDA augments its knowledge of approved additives by reviewing the scientific literature, participating in national and international meetings, and conducting its own research. Because of the controversy surrounding aspartame's approval, FDA has maintained a continuous effort to remain informed of scientific studies that might affect the Agency's present assessment of aspartame's safety.

In the past several years, in addition to our own surveillance of the literature, we have received numerous studies and reports from the NutraSweet Company and the International Life Science Institute (ILSI), relating to the safety of aspartame. I would like to emphasize that these are not studies requested by FDA to answer Agency questions regarding the safety of aspartame. They are studies that are undertaken independent of the Agency and cover issues of interest to the investigators. These interests involve a wide range of topics from investigation of aspartame's breakdown products to the possible effects of aspartame on various parameters of brain function.

Our technical review of the most recent studies we have received is in progress. We have read all but the latest studies and reports submitted to us to determine if there are any which raise possible questions regarding the safety of aspartame. Our preliminary opinion is that none have surfaced. However, as is our usual practice, we are now conducting more detailed reviews of these most recent studies.

At the recent meeting of the First International Meeting on Dietary Phenylalanine and Brain Function in May 1987, two studies were presented that resulted in efforts by the Center to obtain additional information. In one study, Dr. Reuben Matalon et al., of the University of Illinois, discussed results from a clinical study in which plasma levels of phenylalanine were measured in both normal patients and PKU carriers exposed to high dosages of aspartame. In contrast to other studies, the authors report high levels of plasma phenylalanine following aspartame administration in both normal controls and PKU carriers. We look forward to working with Dr. Matalon to review his data and especially to study the methods that were used in his experiments. The methodology will be especially significant since the results do differ noticeably from those of other studies.

A second study was conducted by Dr. Louis Elsas, et al., of Emory University. In this study, PKU carriers were exposed to high levels of supplementary phenylalanine and tested for electroencephalographic (EEG) and neurobehavioral responses. The authors reported a change in brain waves (technically, depression of the mean power frequency of the EEG in one lead), as well as changes in one of the tests of cognitive performance.

As with Dr. Matalon's study, we are extremely interested in working with Dr. Elsas to learn more about his methodology and whether the results are reproducible. Until this opportunity is provided to us, we will be unable to draw any meaningful conclusions from the limited information we now have about either of these studies.

As I have previously described, headache is another type of adverse reaction that has been associated with aspartame use. The NutraSweet Co. has sponsored a study using subjects reporting increased rates of headaches following aspartame exposure. We have not been able to obtain the results of this study but are looking forward to reviewing it in the immediate future since we have been informed that it will apear in the November 5, 1987 edition of the New England Journal of Medicine.

In recent years, there have been a series of studies in animal models reporting an interaction of aspartame with various proconvulsant agents (e.g., electrical current, metrazole, quinolinic acid) to increase seizure occurrence. Certain of these studies appear to demonstrate an additional proconvulsant effect by aspartame while others indicate no influence on seizure activity or even an anticonvulsant effect. Some studies cannot be reproduced in other laboratories. We have concluded that, to date, these studies are not clearly interpretable with regard to the questions of aspartame's influence on seizure occurrence in humans under normal circumstances because of the extremely high doses of aspartame given, the way in which it was administered (such as by oral gavage), and the uncertainties surrounding the comparability of agent-induced seizures in animals and spontaneous incidence of seizures in humans. (As I will indicate in a moment, our own studies in rats with massive doses of aspartame do not indicate to date an association with seizures.)

Unfortunately, many of the questions raised about the safety of aspartame deal with a very speculative and evolving area of the influence of diet on brain chemistry and in turn the effect of changes in brain chemistry on actual brain function. Concepts in this area have changed rapidly and initial speculations have often been found subsequently to be wrong. It is particularly important when dealing with this area of the influence of food components on human behavior that experiments be clearly defined, well controlled and reproducible.

FDA-FUNDED RESEARCH

In addition to the studies undertaken by other organizations and individuals, FDA is supporting research on aspartame safety. We presently have two ongoing research projects and a third study in the developmental stage. The first contract is with Battelle Laboratories for a 3-year study of the influence of high intakes of selected dietary amino acids and aspartame on certain neurochemical relationships in the brain. We expect to begin receiving initial results by mid-1988.

The second ongoing study is being conducted under a 2-year interagency agreement with the National Institute of Environmental Health Sciences. The project entitled, "Dietary Peptides and Behavior," reported that with doses of up to 1000 mg/kg, aspartame has had no significant effect in rats on measures of sensorimotor function, learning and memory or the occurrence of seizures that are produced by repeated low-dose electroshock.

A new study under development with the Federal Aviation Agency (FAA) will assess the effects of aspartame on cognitive tests (e.g., logical reasoning, visual tracking and mental arithmetic) in civilian pilots. The Interagency Agreement has been forwarded to the FAA for their approval.

CONCLUSION

In conclusion, we do not have any medical or scientific evidence that undermines our confidence in the safety of aspartame. This confidence is based on years of study, analysis of adverse reactions, and research in the scientific community, including studies supported by FDA. Otherwise, we would have expected to see a significant incidence of serious and reproducible adverse reactions in view of the tens of millions of our population who consume aspartame products. A significant number of adverse reactions have not been reported, however, despite the enormous publicity that such alleged adverse effects have received in our media.

Nonetheless, we shall remain vigilant and not become complacent in our analysis of research, conduct of research, and review of consumer complaints. Additionally, the Agency will maintain close contact with those who are skeptical of aspartame's safety.

For example, the Center has met with Dr. Richard Wurtman of the Massachusetts Institute of Technology to discuss a number of his hypotheses about aspartame. The Center has also met with the Aspartame Consumer Safety Network to discuss issues relating to aspartame safety, including the status of pending petitions for approval of new uses for aspartame, results of FDA-sponsored research, and improving the exchange of aspartame-related data. We have been pleased to receive their comments regarding the operation of the Center's Adverse Reaction Monitoring System. In addition, Center scientists have presented data on the operation of the ARMS and on the reported aspartame reactions at scientific meetings and to numerous consumer and industry groups.

Therefore, based on the evidence to date, the Agency has concluded that aspartame both in pre and postmarketing, has withstood the requirements of the law that there be reasonable certainty of no harm.

This concludes my formal testimony. I will be pleased to answer any questions you may have.

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: A. Post-Marketing Survey of Aspartame Intake (with charts).

B. Aspartame petitions for use; status of pending petitions.

"A"

The Food and Drug Administration (FDA) has been monitoring Aspartame usage since 1981, when a Post-Marketing Survey (PMS) was instituted as a condition for permitting food additive use. The PMS has two parts: (1) a Poundage Survey, in which the amounts of Aspartame sold to different sectors of the food and pharmaceutical industries are reported and (2) a Dietary Survey, in which the actual ingestion of Aspartame-containing foods is reported for a sample population. Results of each survey have been reported on a quarterly basis.

The Poundage Survey shows that the total amount of Aspartame added to food rose rapidly in 1982 through 1984, but has reached a plateau since 1985. About 75 percent of the total goes into carbonated beverages.

The Dietary Survey reports actual ingestion of Aspartame-containing foods by a sample population of American households. The sample population is a demographically balanced representation of 2000 households (5300 individuals) that is chosen and maintained by a private marketing research firm. This firm's data on food ingestion is combined with amounts of Aspartame in brand-name products to derive estimates of daily Aspartame intake. The daily Aspartame intakes are statistically distributed into groups according to (1) age ranges, (2) types of Aspartame uses, (3) single-day and long-term (14-day average) intakes and (4) special population groups such as: diabetics, persons on weight-reduction diets and women of child-bearing age. The agency has been receiving quarterly reports of Aspartame intake for this sample population since the second quarter of 1984. After a few erratic quarters in which the sample population showed wide swings in Aspartame usage, Aspartame intakes became rather predictable. This indicates that the consumer market for Aspartame-containing foods has settled. Of course, there continue to be seasonal fluctuations.

About 35 percent of the sample population consumes Aspartame-containing foods on a regular basis. The percentage of "Aspartame-eaters" varies with age; 20 percent of toddlers and 30 percent of young children are consumers, whereas 40 percent of adults regularly use Aspartame. Among all Aspartame-eaters, about 20 percent describe themselves as on a weight-reducing diet and seven percent are on a diabetic diet. Because the proportion of pregnant women in the sample population is too small to survey, FDA directed the petitioner to obtain the Aspartame intakes for women of child-bearing age (13-44 years) subdivided into two age ranges: 13-17 years and 18-44 years. After 2 1/2 years of "settled" Aspartame marketing, there are no great differences in how these special population groups consume Aspartame-containing foods in comparison to the entire sample population of Aspartame-eaters. The two special population groups, namely diabetics and weight-reducers, have a greater percentage of Aspartame-eaters than the sample population; that is, 60 percent of diabetics regularly use Aspartame and 50 percent of weight reducers use Aspartame. Specifically, weight reducers ingest 15 percent more Aspartame than the sample population, and those on a diabetic diet ingest about 80 percent more than the sample population. Even with these greater Aspartame intakes, high-frequency diabetic Aspartame eaters ingest only seven percent of the acceptable daily intake and high-frequency weight reducers ingest only four percent of the ADI.

For the entire sample population of Aspartame eaters, the average Aspartame intake is about 50 mg per day, which is less than 1 mg/kg body weight and less than two percent of the ADI. High frequency users of Aspartame-containing foods ingest about 130 mg per day, which is 2 mg/kg body weight and only four percent of the ADI.

Young children have higher rates of Aspartame consumption per unit body weight than adults. For the 2-to-5-year age group, their average intake is three percent of the ADI and high frequency intake is between 4 and 16 percent of the ADI. (We see considerable seasonal variation in the high-frequency ingestion of Aspartame by children.)

In contrast to the PMS intakes that reflect "actual" consumption, the

Agency's premarket estimates of intake represent the potential for petitioned uses of Aspartame and reflect what people can eat. In computing the pre-market estimates we assume that if a food can contain Aspartame, then it does. Such a calculation procedure omits consideration of the fact that most consumers select a variety of foods, some of which contain sweeteners other than Aspartame. We consider pre-market estimates of intake as an upper limit to actual intake. At the present time the PMS intakes are about one-half of our pre-market estimates. This ratio of one-half applies uniformly across all age groups and across all degrees of use of Aspartame foods, (i.e., average and high-frequency consumers).

Finally, one must be cautious about making comparisons of short-term Aspartame intakes to the ADI. Some persist in drawing up hypothetical intakes of Aspartame for a meal or a day in which the individual eats only Aspartame-containing foods. In FDA's pre-market estimates and post-marketing surveillance it is assumed that such occasions are a part of long-term dietary patterns. Therefore, the agency does not compare such short-term intakes to the ADI; rather, it compares these intakes to some other indicator for short-term toxicity. Consideration of the single-day, high-percentile Aspartame intakes in the PMS gives some indication of what consumers may ingest on the short-term basis. Even at 99th percentile of food intake the typical Aspartame consumer has a short-term Aspartame intake that is only 25 percent of the long-term ADI.

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Excerpt from Principles for the Safety of Food Additives and Contaminants in food--pps. 75-85.

ASPARTAME DIETARY PMS

Users as a Percentage of the Total Sample[1]

Quarter (Year)	Total Sample Population		Women Child-Bearing Years	Diabetics	Weight-Reducers
	2-5 Years	All Ages			
2 (1984)		27.7		N/A	N/A
3		32.4		N/A	N/A
4		26.3		52.5	44.5
1 (1985)		30.3		70.8	54.7
2	35.5	36.9		63.8	55.7
3	25.6	35.4		73.7	56.6
4	31.9	35.0		78.1	48.4
1 (1986)	25.5	32.5		58.3	45.3
2	38.4	38.8		69.8	61.9
3	33.3	38.1	45.8	63.8	55.8
4	26.4	33.5	38.5	63.0	48.9
1 (1987)	24.7	32.2	39.9	55.6	52.0
2	33.3	38.8	46.5	64.9	56.0

Annual Summary

July '84-June '85	29.7	31.5	40.1	60.8	52.4
July '85-June '86	30.2	35.4	41.8	70.7	53.2
July '86-June '87[2]	29.4	35.6	42.7	61.8	53.2

[1] Within each population as stated. Data on 14-day averages. Persons that had at least one serving of Aspartame sweetened food in the 14-day survey period. All-ages group.

[2] CFSAN estimated.

ASPARTAME DIETARY PMS

Number of Users & Users as a Percentage[1] of
All Aspartame Eaters

		Women of Child-Bearing Years		Diabetics		Weight-Reducers	
Quarter (Year)	Total Sample Number	Number	% of Total Sample	Number	% Total	Number	% Total
2 (1984)							
3							
4							
1 (1985)							
2							
3	460			42	9.1%	86	18.7%
4	466			50	10.7%	74	15.9%
1 (1986)	421			28	6.6%	81	19.2%
2	503			37	7.4%	117	23.3%
3	489	125	25.6%	30	6.1%	101	20.6%
4	405	104	25.7%	29	7.2%	85	21.0%
1 (1987)	415	119	28.7%	30	7.2%	92	22.2%
2	509	132	25.9%	37	7.3%	108	21.2%

Annual Summary							
July '84-June '85	1,713	495	28.9%	113	6.6%	362	21.1%
July '85-June '86	1,850	487	26.3%	157	8.5%	358	19.4%

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[1] Users on the basis of 14-day average data. Persons that had at least one serving of Aspartame-sweetened food in the 14-day survey period. All-ages group.

ASPARTAME DIETARY PMS

Intakes[1] & Percentages of the Acceptable Daily Intake

AVERAGE INTAKES

Report	Total Sample		Women of Child-Bearing Years		Diabetics		Weight Reducers	
	mg/kg	% ADI	mg/kg	% ADI	mg/kg	% ADI	mg/kg	% ADI
1st Annual Summary July '84-June '85	0.68	1.4%	0.78	1.5%	0.84	1.7%	0.71	1.4%
2nd Annual Summary July '85-June '86	0.84	1.7%	0.90	1.8%	0.93	1.9%	0.88	1.8%
CFSAN Estimated July '86-June '87	0.80	1.6%	0.94	1.9%	1.12	2.2%	0.84	1.7%

90th PERCENTILE INTAKES

Report	Total Sample		Women Child-Bearing Years		Diabetics		Weight Reducers	
	mg/kg	% ADI	mg/kg	% ADI	mg/kg	% ADI	mg/kg	% ADI
1st Annual Summary July '84-June '85	1.6	3.2%	2.0	4.0%	2.1	4.2%	1.6	3.2
2nd Annual Summary July '85-June '86	2.1	4.2%	2.2	4.4%	2.2	4.4%	2.2	4.4
CFSAN Estimated July '86-June '87	2.0	4.0%	2.5	5.0%	3.6[2]	7.2%	2.3[3]	4.5

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[1] 14-Day average intakes; All-ages group, mg/kg body weight.

[2] (3.6/2.0) x 10% = 180%. 90th percentile diabetics ingest 80% more than regular users.

[3] (2.3/3.0) x 100% = 115%. 90th percentile weight reducers ingest 15% more than regular users.

ASPARTAME DIETARY PMS

Toddlers & Young Children

Long-Term Intakes[1] & Percentages of the Acceptable Daily Intake

	0-23 Months			2 5 Years		
Report	Average	90th Percentile	90th as % ADI	Average	90th Percentile	90th as % ADI
1st Annual Summary July '84-June '85	0.81	1.5	3 %	1.3	3.1	6.2%
2nd Annual Summary July '85-June '86	1.9	3.3	6.6%	1.7	4.8	9.6%
CFSAN Estimated July '86-June '87	1.8	2.7	5.4%	1.5	3.8	7.6%

Single-Day Intakes[2]

	0-23 Months		2-5 Years	
Report	Average	90th Percentile	Average	90th Percentile
1st Annual Summary July '84-June '85	4.7	11	5.1	11
2nd Annual Summary July '85-June '86	9.6	22	6.7	13
CFSAN Estimated July '86-June '87	8.2	20	6.2	11

[1] 14-Day average intakes; mg/kg body weight.

[2] mg/kg body weight

Environmental Health Criteria 70

Principles for the Safety Assessment of Food Additives and Contaminants in Food

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If evidence of widespread intolerance to a food additive appears in a country that permits its use, procedures should be established for the centralized reporting of such information, if one is not already in place. Medical professionals should be alerted, and appropriate medical tests performed on affected individuals to determine the nature of intolerance. If the problem arises with an additive previously considered and given an ADI by JECFA, ideally the results will be relayed to the Committee so that the safety of the additive can be reconsidered. Remedies may range from no action to a recommendation that the additive be removed from the market. Factors, such as its natural occurrence in food, should be taken into account in such deliberations. Because food intolerance is not spread throughout the general population, but is restricted to small subpopulations or individuals, one of the usual remedies is to label the food containing the additive prominently, so that sensitive individuals can avoid it.

5.5 Setting the ADI

Almost any substance at a high enough test level will produce some adverse effect in animals. Evaluation of safety requires that this potential adverse effect be identified and that adequate toxicological data be available to determine the level at which human exposure to the substance can be considered safe.

At the time of its first meeting, JECFA recognized that the amount of an additive used in food should be established with due attention to "an adequate margin of safety to reduce to a minimum any hazard to health in all groups of consumers" (9, pp. 14-15). The second JECFA, in outlining procedures for the testing of intentional food additives to establish their safety for use, concluded that the results of animal studies can be extrapolated to man, and that

> "some margin of safety is desirable to allow for any species difference in susceptibility, the numerical differences between the test animals and the human population exposed to the hazard, the greater variety of complicating disease processes in the human population, the difficulty of estimating the human intake, and the possibility of synergistic action among food additives" (10, p. 17).

This conclusion formed the basis for establishing the "acceptable daily intake", or ADI, which is the end-point of JECFA evaluations for intentional food additives. In the context in which JECFA uses it, the ADI is defined as an estimate (by JECFA) of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.

The ADI is expressed in a range, from 0 to an upper limit, which is considered to be the zone of acceptability of the substance. JECFA expresses the ADI in this way to emphasize that the acceptable level it establishes is an upper limit and to encourage the lowest levels of use that are technologically feasible.

Substances that accumulate in the body are not suitable for use as food additives (39, p. 8). Therefore, ADIs are established only for those compounds that are substantially cleared from the body within 24 h. Data packages should include metabolism and excretion studies designed to provide information on the cumulative properties of food additives.

JECFA generally sets the ADI of a food additive on the basis of the highest no-observed-effect level in animal studies. In calculating the ADI, a "safety factor" is applied to the no-observed-effect level to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive animal species, i.e., the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmacokinetic data are available establishing that the test in the other species is more appropriate for man (section 5.5.1).

Generally, the ADI is established on the basis of toxicological information and provides a useful assessment of safety without the need for data on intended or actual use and consumption. However, in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed. Therefore, general information about exposure patterns should be known at the time of the safety assessment (section 5.5.6). For example, if a food additive is to be used in infant formulae, the safety assessment is not complete without looking carefully at safety studies involving exposure to very young animals.

JECFA uses the risk assessment process when setting the ADI, i.e., the level of "no apparent risk" is set on the basis of quantitative extrapolation from animal data to human beings. Generally, JECFA does not undertake risk management, in that it leaves it to national governments to use the quantitative assessments in a manner appropriate to their own situations. However, this has not always been the case, in that sometimes JECFA has taken into consideration, in peripheral ways, benefits (e.g., hydrogen peroxide as an alternative to pasteurization in developing countries (12; 21)) and economic need (e.g. polymer packaging materials that contain potentially hazardous migrants should be limited to situations where no satisfactory alternatives exist (1)). In this context, risk assessment and risk management are more broadly used than, e.g., they are often used in the context of carcinogenesis.

5.5.1 *Determination of the no-observed-effect level*

A determination of a no-observed-effect level for a study depends primarily on the proper selection of doses, such that the highest dose produces an adverse effect that is not observed at the lowest dose. Several dose levels are used to determine the dose-effect relationship. Knowing the nature of the toxic response to a compound at the high level, a more confident assessment of a no-observed-effect level at the lower test levels can be made by focusing more clearly on the target tissues. Great care must be taken in dose selection, because the no-observed-effect level must be one of the experimental doses; it is not an inherent property of the animal system. For a discussion of items to consider when selecting doses, see reference 75, pp. 9-49.

The following discussion concerns the performance of long-term studies, because these studies are the type most often performed in support of intentional food additives, and they give rise to much controversy. However, 90-day studies are sometimes sufficient for establishing safety, as, for example, with substances that are closely related to food additives of known low toxicity (section 5.5.4). Many of the points discussed below in relation to long-term studies are also appropriate for shorter studies when such studies serve as the basis for safety determinations.

When long-term studies are indicated, short-term range-finding studies should first be performed to ensure the proper selection of dosage regimen. Care must be taken in applying this approach to dose level selection, because doses that produce signs of toxicity in short-term testing may be reversible on more long-term exposure. In such situations, the highest dose selected from range-finding studies may not produce an adverse effect with long-term exposure, precluding a determination of the no-observed-effect level in the longer study (the significance of this transient effect should be taken into account when evaluating the data). A situation of perhaps greater frequency is one in which the dosages in the long-term study are too high, so that, even the lowest dose results in adverse effects, and a no-observed-effect level cannot be established.

Ideally, in a long-term study, the high-dose level should be sufficiently high to elicit signs of toxicity without causing excessive mortality or some exaggerated pharmacological effect, such as sedation. Although doses of non-nutritive additives as high as 5% of the total diet do not always produce adverse effects, higher doses should not be tested, because they may produce a significant nutritional imbalance. Therefore, if no adverse effects are observed at 5% of the diet, this dose should be considered the no-observed-effect level. On the other hand, nutritive additives may be fed at higher doses as long as the nutritional balance is effectively preserved in both the test animal and controls (section 6.2.3).

Ordinarily, the middle dose should be selected to be sufficiently high to elicit minimal toxic effects or it should be set midway between the high and low doses. However, if significant differences exist in the pharmacokinetic or metabolic profile of the test substance between the high and low doses, then an additional dose should be included in the study to provide more assessment points.

The lowest dose should not interfere with morphology, development, normal growth, or longevity or produce adverse functional alterations.

The determination of an adverse effect in a particular study depends on the doses tested, the types of parameters measured, and the ability to distinguish between real adverse effects and false positives. If, for example, only a slight change in a particular parameter is noted at the highest dose that is not observed at the lower doses, then it is difficult to distinguish between a real adverse effect and a spurious positive finding. In addition, a reduction in body-weight gain coupled with decreased food consumption is difficult to interpret as an adverse effect, because palatability of the chow might be affected by the presence of high levels of the test compound. However, as noted in section 5.1.1, generalized decrement in weight gain has sometimes been used for setting an effect level in the absence of other toxic manifestations.

When two or more studies are performed on an additive in different animal species, no-observed-effect levels are calculated from each study. The overall no-observed-effect level used for calculating the ADI is the no-observed-effect level from the animal study that displayed a toxic effect at the lowest dose. The species on which this study was performed is then considered to be the most sensitive species. This approach is reasonable when the animal studies are of similar length (in relation to the expected life span of the species) and quality, and no other data relating to this issue are available. However, if the quality of one study is obviously superior to the others and/or the studies differ with respect to length (long-term versus short-term), extra weight should be given to the longer better-quality studies when determining the overall no-observed-effect level. If metabolic and pharmacokinetic data are available, the species most similar to man with respect to the toxic effect should be used in calculating the overall no-observed-effect level, rather than the most sensitive species.

5.5.2 *Use of the safety factor*

The safety factor has been used by JECFA, since its inception [illegible] is intended to provide an adequate margin of

safety for the consumer by assuming that the human being is 10 times more sensitive than the test animal and that the difference of sensitivity within the human population is in a 10-fold range. In determining an ADI, a safety factor is applied to the no-observed-effect level determined in an appropriate animal study.

JECFA traditionally uses a safety factor of 100 (10 x 10) in setting ADIs based on long-term animal studies, i.e., the no-observed-effect level is divided by 100 to calculate the ADI for an additive. The no-observed-effect level is usually expressed in terms of mg compound per kg body weight per day, and the ADI is expressed in the same units. A food additive is considered safe for its intended use if its human exposure is less than, or is approximately, the same as the ADI. The ADI generally includes both its natural occurrence and deliberate addition to food (17, pp. 8-10), except when the substance occurs naturally in a chemical form different from that employed as a food additive, or when its natural occurrence was not considered when setting the ADI and the substance naturally present in the diet contributes significantly to its total intake (as with nitrates). Because in most cases, data are extrapolated from lifetime animal studies, the ADI relates to life-time use and provides a margin of safety large enough for toxicologists not to be particularly concerned about short-term use at exposure levels exceeding the ADI, providing the average intake over longer periods of time does not exceed it.

National governments are responsible for regulating food additives in such a way that consumption from natural occurrence and deliberate addition to food does not exceed the ADI for each additive that is permitted. As stated by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (2, p. 6), "it is desirable that national governments should maintain a check on the total intake of each food additive, based on national dietary surveys, to determine whether the total load in the diet approaches the acceptable daily intake." Individual governments have the discretion of determining whether they will base their regulatory decisions on the "average" consumer or the "high" consumer of food additives.

A safety factor of 100 should not be considered immutable. When setting the ADI, various test data and judgemental factors should be considered. These include:

(a) Inadequate data base

In this case, a larger safety factor may be appropriate (section 5.5.5).

(b) Reversibility of the observed effect in embryotoxicity studies

If irreversible developmental effects, such as skeletal abnormalities (as opposed to retarded skeletal growth), are seen in the fetuses of animals administered the substance *in utero*, a study on a second species is indicated. If similar irreversible effects are not confirmed in the second animal species, pharmacokinetic studies would be useful to determine relevance to human beings. Judgement would then be needed to set an appropriate safety factor. If frank teratogenic effects are observed in both studies, judgement would be needed to decide whether either a larger safety factor should be considered or it should be recognized that the use of the substance as a food additive is not appropriate. If only reversible developmental effects are seen, such as retarded skeletal and soft tissue development or decreased fetal weight, the usual safety factor of 100 may be applied.

(c) Age-related effects in reproduction studies

Such studies may demonstrate different toxic responses in young animals compared with older ones. Metabolic studies may demonstrate that the differences in sensitivity are due to such factors as incomplete development of enzyme systems used for metabolizing xenobiotic compounds or differences in intestinal flora. Safety factors should be set on the basis of the target population. If young children are likely to consume the additive, the ADI should be based on the no-observed-effect level from the phase of the study in which young animals were exposed, if the no-observed-effect level was lower than in the adult phase. If, on the other hand, it is shown that children will not be exposed to the additive, it may be appropriate to set the ADI on the basis of the no-observed-effect level established in the adult phase of the study.

(d) Finding of carcinogenicity

Carcinogens vary in the magnitude of risk they present for man, because they act via different mechanisms. Even though no basis exists for the exact extrapolation of risk from experimental animals to man, the degrees of risk from different carcinogens can often be inferred from the data. However, with the present state of knowledge, it would be appropriate to consider the use of a carcinogenic substance as an intentional food additive only under very restricted circumstances. For example, if cancer is shown to be a secondary effect, such as bladder tumours occurring secondary to the induction of bladder stones, and there is evidence of a threshold below which the

additive is safe, then it would be appropriate to use a safety factor for determining the safe level of use of the additive. Under extenuating circumstances, such as an unambiguous demonstration that the health benefits exceed the risk, it may also be possible to use a carcinogenic additive.

(e) If reasons exist for setting a lower safety factor

If toxicity and dose-response effects in human beings are known, such data should take precedence over extrapolation from animal studies; a 10-fold safety factor would be appropriate if there is no evidence that human sensitivity to the agent varies more than 10-fold among individuals. A lower safety factor may also be appropriate when the additive is similar to traditional foods, is metabolized into normal body constituents, and/or lacks overt toxicity. Also, a 100-fold safety factor often would not provide a high enough level of nutrients required to satisfy nutritional needs and to maintain health (toxicity for some essential nutrients such as Vitamin A, Vitamin D, certain essential amino acids, and iron may be reached at levels less than 10 times higher than those recommended for optimal nutrition). A substance that serves as a significant source of energy in the human diet obviously cannot fit into the constraints of a 100-fold safety factor.

The use of standardized safety factors based on no-observed-effect levels for establishing the acceptable level of use of food additives is a crude procedure, given the known wide variability in toxic responses. For example, the nature of the dose response usually is not used. In part, this is a reflection of the fact that good dose-response data are not available for many compounds. Attempts to use the dose-response behaviour of compounds in establishing quantitative end-points must contend with this limitation.

In the broadest sense, the procedures used by JECFA take into account the nature of the biological effects observed in animal bioassays only to the extent that a distinction is made between carcinogens and non-carcinogens, i.e., ADIs are established for non-carcinogens, while most carcinogens are considered to unacceptable for use as intentional food additives. Otherwise, the nature of the observed effect is not an explicit component of the quantitative assessment of food additives. However, the nature of the effect and a determination of its significance are often implicitly considered by scientists, when reviewing the data.

JECFA should take these and other factors into account when determining acceptable daily intakes of food additives. However, in situations in which little is known beyond the empirical finding of toxicity in animal studies, the traditional approach for calculating ADIs would seem to be appropriate. This may be an issue for future consideration by JECFA.

5.5.3 *Toxicological versus physiological responses*

When analysing a toxicological study and setting a no-observed-effect level, a distinction must be drawn between reversible changes that are due entirely to normal physiological processes or homeostasis-maintaining mechanisms, and to toxic responses themselves (section 5.1). Examples of the former include: laxative effects from osmotic or faecal overload, liver hypertrophy and microsomal enzyme induction from high doses of substances metabolized by the liver, decreased body weight gain or caecal enlargement from high levels of non-nutritive substances, alteration in renal weight that is directly related to the amount of water being processed by the kidney, and decreased growth rate and food consumption related to the dietary administration of an unpalatable substance. However, care must be taken in interpreting these changes, and they should not automatically be dismissed as being unimportant from a toxicological point of view. For example, microsomal enzyme induction in the liver may result in alterations in the metabolism of compounds unrelated to the administered substance, which could result in a toxic effect. A decrease in the rate of body-weight gain coupled with a corresponding reduction of food intake could be due to toxic anorexia, rather than a palatability defect.

The dose at which the effect occurs should be compared with the amount of the substance consumed by human beings. Thus, it would ordinarily be acceptable to permit the use of a substance that causes diarrhoea only at very high levels of consumption in rats, but the use of such a substance should be severely restricted or not permitted if it causes diarrhoea at normal levels of consumption in human beings. Sometimes, physiological adaptation may progress through overload to frank toxicity.

Further studies are indicated in situations in which it is difficult to draw a clear distinction between a toxic and a physiological response. Special studies such as paired feeding, caloric balance comparisons between food consumption and body-weight gain, or, in the case of reproduction studies, cross fostering, can be performed to decide issues such as reduced food intake and reduced body-weight gain related to unpalatable test substances. Metabolic and pharmacokinetic studies may be of use in providing information on the distribution of the test compound and its metabolites or the dose at which a change in metabolism occurs.

5.5.4 *Group ADIs*

If several compounds that display similar toxic effects are to be considered for use as food additives, it may be appropriate in establishing an ADI to consider the group of compounds

in order to limit their cumulative intake. For this procedure to be feasible, the additives must be in the same range of toxic potency. Flexibility should be used in determining which no-observed-effect level is to be used in calculating the ADI. In some cases, the average no-observed-effect level for all the compounds in the group may be used for calculating the group ADI. A more conservative approach is to base the group ADI on the compound with the lowest no-observed-effect level. The relative quality and length of studies on the various compounds should be considered when setting the group ADI. When the no-observed-effect level for one of the compounds is out of line with the others in the group, it should be treated separately.

When considering the use of a substance that is a member of a series of compounds that are very closely related chemically (e.g., fatty acids), but for which toxicological information is limited, it may be possible to base its evaluation on the group ADI established for the series of compounds. This procedure can only be followed if a great deal of toxicological information is available on at least one member of the series and if the known toxic properties of the various compounds fall along a well-defined continuum. Interpolation, but not extrapolation, can be performed by this procedure. The use of this procedure by JECFA represents one of the few situations in which the Committee has used structure/activity relationships in its safety assessments.

In some instances, group ADIs can be established primarily on the basis of metabolic information. For example, the safety of esters used as food flavours could be assessed on the basis of toxicological information on their constituent acids and alcohols, provided that it is shown that they are quantitatively hydrolysed in the gut.

The calculation of a group ADI is also appropriate for compounds that cause additive physiological or toxic effects, even if they are not closely related chemically. For example, it may be appropriate to establish a group ADI for additives such as bulk sweeteners that are poorly absorbed and cause laxation.

5.5.5 *Special situations*

There are occasions when JECFA considers the use of an ADI in numerical terms not to be appropriate. This situation arises when the estimated consumption of the additive is expected to be well below any numerical value that would ordinarily be assigned to it. Under such circumstances, JECFA uses the term "ADI not specified". The Committee defines this term to mean that, on the basis of available data (chemical, biochemical, toxicological, and other), the total daily intake of the substance, arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food, does not, in the opinion of the Committee, represent a hazard to health. For that reason, and for the reasons stated in the individual evaluations, the establishment of an ADI in numerical form is not deemed necessary (e.g., 1, Annex II). An additive meeting this criterion must be used within the bounds of good manufacturing practice, i.e., it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance (16, pp. 10-11). That the background occurrence of the chemical must be taken into account in the evaluation of its safety was articulated by the WHO Scientific Group on Procedures for Investigating Intentional and Unintentional Food Additives (2, p. 7).

JECFA has encountered several situations in which either the body of data before it on a new additive was limited, or the safety of a food additive for which the Committee previously assigned an ADI was brought into question by the generation of new data. When the Committee feels confident that the use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but is not confident that its use is safe over a lifetime, it often establishes a "temporary" ADI, pending the submission of appropriate data to resolve the safety issue on a timetable established by JECFA. When establishing a temporary ADI, the Committee often uses a higher-than-usual safety factor, usually increasing it by a factor of 2. The additional biochemical and toxicological data required for the establishment of an ADI are clearly stated, and a review of these new data is conducted before the expiration of the provisional period.

This approach seems to have worked reasonably well in practice in that it has encouraged necessary research without creating any known safety problems. In many cases, long-term studies are requested, but timetables are not met, which means that JECFA has had to extend temporary ADIs for long periods of time. JECFA has withdrawn ADIs, in instances where data were not forthcoming, as a safety precaution.

5.5.6 *Comparing the ADI with potential exposure*

When establishing ADIs, collateral exposure information is often useful for determining the relationship between the two values. The agreement between exposure and acceptable daily intake helps to determine whether an "ADI not specified" should be established. Exposure information is also indispensable when:

(a) performing risk assessments for food contaminants and processing aids; and

(b) assessing the safety of added substances that may be naturally present in food to determine their relative contributions to the diet (17, pp. 8-10).

In order to accurately compare exposure and acceptable intake, similar assumptions should be used for making each estimate or, at least, the differences and similarities in the estimates should be understood. For example, if an ADI is computed from lifetime dosage, then the estimated human exposure should represent lifetime exposure to the additive. Sometimes, acceptable intakes are computed for specific age groups or for certain dosage conditions when short-term exposure should be limited, such as with certain food additives that cause laxative effects at high dose levels. Under such circumstances, the estimated human exposure should represent the same age group or dosage conditions. In practice, however, estimates of exposure do not represent exposure for individual consumers in the same way that toxicological data represent dosages for individual animals. Data bases on food and food additive intakes provide composite data for subpopulations, such as the average dietary habits of a particular nation's population.

For effective comparison of exposure estimates with acceptable intakes, the assumptions used to compute exposure estimates should always be stated. Data on the functional use(s) of intentional food additives and information on approaches used to compute intake estimates, such as analytical studies on food constituents or migration (carry-over) models for certain contaminant situations, should be provided if possible.

Each estimate of exposure represents a facet of actual human exposure and, thus, each estimate represents useful scientific data. However, it is not possible to describe specific procedures for estimating exposure for all food additive and contaminant situations. However, JECFA is able to provide guidance by describing the types of estimation procedures that have been accepted by previous Committees, which are discussed in section 3.1.1

"B"

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ASPARTAME PETITONS FOR USE; STATUS OF PENDING PETITIONS

1. A list of approved petitons for use and petitions filed that are pending approval.
2. Status of pending petitions for additional uses.

ASPARTAME PETITIONS

REGULATED

FAP No.	Petitioner	Use	Date Received	Date Filed	Date Regulated
3A2885	G.D. Searle & Co.	Original petition - table top sweetener and various dry products	2-12-73	2-27-73	7-26-74 10-22-81[1]
2A3661	G.D. Searle & Co.	Carbonated Beverages	8-24-82	9-8-82	7-8-83
2A3662	Rexall Corp.	Chewable Multivitamins	8-20-82	9-8-82	5-30-84

UNDER REVIEW

FAP No.	Petitioner	Use	Date Received	Date Filed	Date Regulated
3A3694	Coca-Cola	Refrigerated Juice based Beverages, Frozen Concentrates and Confections	12-9-82	1-3-83	11-28-86[2]
3A3695	Tropicana	Chilled Juice based drinks	12-13-82	1-3-83	11-28-86[2]
3A3744	G.D. Searle & Co.	Bulk packaging	7-13-83	7-27-83	____
4A3766	Shaklee Corp.	Breath mints	11-16-83	12-8-83	11-28-86[2]
4A3769	Thomas J. Lipton	Iced Tea	12-16-83	1-20-84	11-28-86[2]

[1] October 22, 1981 is the date the regulation (§172.804) for Aspartame was reinstated.

[2] Regulations published on this date but agency response to objections to the regulations is pending.

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FAP No.	Petitioner	Use	Date Received	Date Filed	Date Regulated
4A3775	Bernard Foods	Ready to eat gelatin	12-30-83	1-20-84	____
5A3829	Squirt & Co.	Aseptically packaged fruit juice based drinks	10-3-84	10-25-84	____
5A3861	Pfizer Central	Frozen Desserts	4-18-85	5-13-85	____
5A3874	Foodways National	Frozen cheesecakes, fruit cups and toppings	6-7-85	6-28-85	____
6A3912	Holland American Wafer Co.	Wafer cookies	1-15-86	6-18-86	____
6A3942	Canandaigua Wine Co.	Wine Coolers	5-22-86	6-18-86	____
6A3945	Milk Ind. Foundation; Beatrice Dairy Prod. and NutraSweet Co.	Flavored Milk Beverage	6-9-86	6-18-86	____
6A3963	NutraSweet Co.	Fruit spreads, toppings	8-25-86	8-29-86	____
6A3964	Milk Ind. Foundation; Beatrice Dairy Prod. and NutraSweet Co.	Yogurt products	9-12-86	9-17-86	____
7A4014	Foodways National, Inc. and Nutrasweet Co.	Frozen dairy and non-dairy frostings, toppings & fillings.	7-6-87	7-8-87	____
7A4015	NutraSweet Co.	Hard candies, and cough drops	7-7-87	7-21-87	____
7A4029	Stroh Brewery Co.	Malt Coolers	8-10-87	8-17-87	____
7A4044	NutraSweet Co.	Baked goods & baking mixes	9-24-87	10-15-87	____

Aspartame

Date Received	Petn No.	Petitioner	Use	Status
12-9-82	3A3694	Coca-Cola Co.	Juice Bev.	Objections received requesting a stay and hearing based on CNI petition (seizure & eye damage), change from 99 to 90th, and Pardridge letter to the editor 1/2/87. Draft document under administrative review.
12-13-82	3A3695	Tropicana	Juice Bev.	Same as 3A3694
7-13-83	3A3744	Searle & Co.	Bulk	Reject letter being prepared.
11-16-83	4A3766	Skaklee Corp.	Breath Mints	Same as 3A3694
12-16-83	4A3769	Thomas J. Lipton	Chilled ice tea Bev.	Same as 3A3694
12-30-83	4A3775	Bernard Food	Ready to eat Gelatin	Draft FRD being circulated for tech. review.
10-3-84	5A3829	Squirt Co.	Non-refrig. F. Juice bev.	FRW copy being held for final approval.
4-18-85	5A3861	Pfizer Central Research, Pfizer Inc.	Frozen Deserts	Same as 4A3775
6-7-85	5A3874	Foodways National	Frozen cheese cakes, fruit cups & toppings	Data on the Chem. stability APM in fruit cups and toppings and validation data for degradation products received 9/4/86; HFF-415 reviewing. Needs final Tox. memo
1-15-86	6A3912	Holland American Wafer Co.	Wafer Cookies	Needs final Tox. memo.

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Date Received	Petn No.	Petitioner	Use	Status
5-22-86	6A3942	Canandaigua Wine Co.	Wine Coolers	Same as 4A3775
6-9-86	6A3945	Milk Ind. Foundation Beatrice Dairy Products, NutraSweet Co.	Flavored Milk Bev.	Same as 4A3775
8-25-86	6A3963	NutraSweet Co.	Fruit spreads, toppings & syrups	Reject letter sent 5/28/87. Requested use levels in toppings and syrups & AMP degradation products found in these products at room temperature (Rec. 7/13/87).
9-12-86	6A3964	Beatrice Foods Co., NutraSweet, & Milk Ind. Foundation	Yogurt like Products	Same as 4A3775
7-6-87	7A4014	Foodways National, Inc. and NutraSweet Co.	Frozen dairy and non-dairy frostings, toppings and fillings.	Being reviewed by HFF-158, HFF-415, and HFF-304
7-7-87	7A4015	NutraSweet Co.	Hard candies and cough drops.	Reject letter sent 9-16-87 (Chem. info).
8-10-87	7A4029	Stroh Brewery	Malt Coolers	Same as 7A4014
9-24-87	7A4044	NutraSweet Co.	Baked goods and baking mixes.	Same as 7A4014

STATUS OF EXTRAMURAL PROJECTS RE: ASPARTAME

The FDA is actively engaged in developing appropriate test models with which to evaluate potential affects of food additives on the nervous system. As part of this effort the FDA is currently sponsoring three extramural projects investigating central nervous system neurochemical and behavioral function:

1. A three year contract (#223-86-2095) for $678,772 was awarded September 30, 1986, to Battelle Memorial Institute, Columbus Division. This project, entitled "Dietary Amino Acids and Brain Function" studies consequences of altered amino acid balance on neurochemistry, particularly neurotransmitters in animals.
2. A two year Interagency Agreement (#224-87-2436) for $92,440 was initiated February 19, 1987, with the National Institute for Environmental Health Sciences, Research Triangle Park. This project, entitled "Dietary Peptides and Behavior" studies effects of changes in amino acid balance on seizure threshold or other neurobehavioral function in animals.
3. A two year Interagency Agreement (#224-88-2435) for $99,390 was initiated October, 1987 with the Federal Aviation Administration, Oklahoma City. This project, entitled "Effects of Aspartame and Related Compounds on Human Performance" studies effects of ingestion of aspartame by volunteer humans on performance in tests of cognitive function.

Status of Battelle contract (#223-86-2095)

The overall objectives include the following:

1. to develop an experimental rodent model which will enable the detection and interpretation of diet-induced changes in brain function,

2. to determine the extent to which the ingestion of aspartame and other related compounds, which might alter amino acid balance, may affect brain neurotransmitter functions, and

3. to determine whether the treatment-related neurochemical changes, if any, are dependent upon such experimental conditions as route or duration of administration, nutritional status, sex or circadian cycle.

The contractor has developed and submitted a detailed scientific plan describing the experiments to be conducted. The final draft of this plan is being reviewed for approval by the Project Advisory Group. The contractor has proceeded with development and validation of the neurochemical methodology to be used and standard operating procedures in compliance with Good Laboratory Practices.

Status of the NIEHS Interagency Agreement (#224-87-2436)

Under this Interagency Agreement, the NIEHS is to evaluate the changes in brain excitability and behavior of adult and developing animals exposed acutely or repeatedly to compounds which may alter the endogenous levels of neurotransmitter precursors. Endpoints are to include measures of seizure proneness, particularly with regard to electrically kindled seizures, sensorimotor reactivity, and cognitive function. Comparisons of intraperitoneal vs. intragastric dosing are to be made. Depending on the outcome of these initial experiments, further studies will be conducted using specific amino acids e.g. phenylalanine and aspartic acid.

A series of experiments have already been completed. Acute intragastric administration of aspartame in doses up to 1,000 mg/kg had no significant effect on routine measures of sensorimotor function, including acoustic startle response, prepulse inhibition of startle, or spontaneous motor activity. These tests have been used frequently to assess chemical-induced alterations in central nervous system arousal and behavioral reactivity to environmental stimulation. Similar doses were found to have no significant effect in two different tests of learning and memory. Aspartame at total doses of up to 2,000 mg/kg was also found to have no significant effect on threshold of electrically kindled seizures.

Intraperitoneal administration of aspartame at doses up to 500 mg/kg had no effect on spontaneous motor activity.

Repeated daily dosing (14 days) with aspartame at doses up to 1,000 mg/kg/day revealed no effects on either spontaneous motor activity or learning behavior.

Status of the Interagency Agreement with the FAA (#224-87-2435)

This is a new Interagency Agreement (IAG) with the Federal Aviation Administration (FAA). Responding to an American Medical Association recommendation, the FAA currently has contracts with three research centers for testing cognitive performance in pilots. The test sites are the Institute of Aviation Medicine at the University of Illinois, Champaign, IL, Wright Civil Aeronautic Medical Research Center, Dayton, OH, and the Department of Neurology, Georgetown University, Washington, DC. Each center has a core of cognitive tests (e.g. logical reasoning, visual tracking, mental arithmetic) and additional tests emphasizing each centers' particular strengths (e.g. EEG recordings, flight performance tests using simulators). Tests are being validated against responses of individuals with diagnosed organic brain dysfunction.

This IAG allows additional tests for effects of acute ingestion of aspartame (up to the allowable daily intake, 50 mg/kg) in those same subjects. The high precision in performance of these subjects maximizes the sensitivity of the tests. The design uses each individual as their own control, and includes testing of placebo, phenylalanine, or other physiological agents (e.g. ethanol, caffeine) which have previously been shown to affect performance in these tests (positive controls).

Depending on initial results, subsequent tests will investigate dose-response relationships, chronic aspartame ingestion, co-ingestion of aspartame with other dietary components (or amino acids), and/or tests in PKU heterozygotes and the general population.

Senator METZENBAUM. Dr. Young, thank you very much for being with us. It is always a pleasure to have you testify before us and to work with you.

Are you personally satisfied with the credibility of the key scientific tests used to approve NutraSweet?

Commissioner YOUNG. I have looked at that very extensively. There is no question that there was controversy around the time of the approval process. I went through study by study and listened carefully to what the Center told me. Obviously, I was not there at that time, but based on the records, though there were flaws in particular studies, the weight of evidence supports the action that the agency took.

I think also we have to look at it in a time tunnel of where we were. We now have good laboratory practices and good manufacturing practices which were not in place at that time. Based on the history at that moment, I am satisfied with the integrity of the studies despite the controversy that was associated with it and the fact that some studies had to be disregarded.

I see the process as being carefully followed, and as near as I could tell, the conclusion was valid.

Senator METZENBAUM. In the history of the FDA, has there ever been any other case in which the scientific data submitted to the FDA caused the FDA to be so concerned about the representations made to it that it was sent to a U.S. Attorney for presentment to a grand jury for indictment—any other case?

Commissioner YOUNG. I would like to ask my Counsel, Tom Scarlett, that, who would be able to handle that legal detail, because I am not sure in the FDA legal history of over 75 years whether we had any case analogous to this.

Mr. SCARLETT. It is not uncommon for the FDA to refer incidents of scientific misconduct for criminal investigation. I think the Senator is asking about a specific type of scientific misconduct or poor study execution, and I cannot state whether or not that is the only instance similar to this, and I will check and send something for the record.

[Information supplied follows:]

Submission for the Record

ASPARTAME

Tuesday, November 3, 1987

United States Senate
Committee on Labor and Human Resources
Washington, D.C.

SUBMISSION: General Counsel opinion on cases, similar to aspartame, which were referred by FDA to the Department of Justice for consideration of criminal charges because of irregularities in reporting of test data.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Office of the General Counsel
Food and Drug Division
Rockville, MD 20857

December 22, 1987

The Honorable Howard M. Metzenbaum
United States Senate
Washington, D.C. 20510

Dear Senator Metzenbaum:

During the November 3 hearing on aspartame you asked:

> In the history of the FDA, has there ever been any other case in which the scientific data submitted to the FDA caused the FDA to be so concerned about the representations made to it that it was sent to a U.S. Attorney for presentment to a grand jury for indictment--any other case? ... it is my understanding--I think this occurred in 1977--that prior to that time, there had never been a case in which the submissions of a company to the FDA had provided a basis to submit their file, their record, to the U.S. Attorney for submission to a grand jury, and that since then there has certainly been none. Is that correct?

I have discussed this question with members of my staff and FDA's compliance staff. There was at least one case referred by FDA to the Department of Justice for consideration of criminal charges because of irregularities in the reporting of test data. The case involved the drug MER-29 and was referred some time in the 1960's. There were also several referrals involving questionable data generated by clinical investigators.

The Honorable Howard M. Metzenbaum
December 22, 1987
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One clarification needs to be made. Your question could be misunderstood as suggesting that the data on the testing of aspartame formed the principal basis for FDA's referral to the United States Attorney. In fact, the referral was mainly based on studies relating to other products, although the referral letter identified concerns about the aspartame data.

I request that this letter be made part of the hearing record.

Sincerely yours,

Thomas Scarlett
Chief Counsel

Senator Metzenbaum. Well, it is my understanding—I think this occurred in 1977—that prior to that time, there had never been a case in which the submissions of a company to the FDA had provided a basis to submit their file, their record, to the U.S. Attorney for submission to a grand jury, and that since then there has certainly been none. Is that correct?

Mr. Scarlett. It is probably correct, but I cannot state definitely.

Senator Metzenbaum. All right.

Dr. Young, do you believe that NutraSweet is composed of building blocks, just like those found in fruits, vegetables and meats, and that our bodies treat them no differently than if they came from a glass of milk or string beans?

Commissioner Young. To the best of my knowledge, that is correct. I think it is important to point out that on the daily consumption data that we have, that one of the building blocks, phenylalanine, which is most extensively talked about, has a level of 83 milligrams per kilogram from ordinary protein as compared to 1 to 2 for the comparable amount in aspartame.

Based on digestive studies, I would expect that a molecule as I showed you would be broken down very rapidly to its components. It is a small dipeptide; there may be actual transport of that into the human being, but it should be broken down primarily to the building blocks. This is natural as contrasted to the many artificial substances that we add to our food and drug supply.

So I believe that it would be broken down to its components, methanol, phenylalanine, and aspartic acid.

Senator Metzenbaum. I have one last question. United Press International—let me quote from a recent UPI investigative series on NutraSweet—"United Press International has learned that more than 10 Federal officials involved in the NutraSweet review have taken private sector jobs linked to the industry; among them, Hayes, an Acting FDA Commissioner, and former chiefs and acting chiefs of the agency's Bureau of Foods. Between 1979 and 1982, four FDA officials who participated in the approval process took jobs linked to the NutraSweet industry: Pape; Acting FDA Commissioner Sherwin Gardner; Albert Kolbye, who was Associate Director for Toxicology, and Mike Taylor, an FDA lawyer who represented the Bureau before the Board of Inquiry. All four denied any conflict of interest." End of quote.

What we have here is not a legal conflict [illegible] interest, but a revolving door, where many of the key decisionmakers on NutraSweet later go to the industry, where the regulators end up taking jobs with the firms that were regulated.

We know of the revolving door syndrome, which we talk about so much in the Department of Defense. Is this also applicable in this instance, and particularly applicable with respect to the matter of NutraSweet?

Commissioner Young. Let me answer in general and then specifically. FDA has the responsibility of overseeing approximately $550 billion worth of industry per year. That is 25 cents on every consumer dollar. Since there has to be in many instances someone finding employment after leaving government, it is not unlikely that some of these individuals will go into industry and not back to academe. In particular there were individuals that were involved in the NutraSweet question who did seek jobs in industry or more far-removed; in the case of Sherwin Gardner, of the Grocery Manufacturers of America, which is a trade association, if you will, his work is certainly not directly related. Others have been more related in particular law firms. In the case of Dr. Hayes, it was really a consultancy.

If one looks at this in its broadest sense—and I believe the GAO focused on this—there was not any actual conflict of interest. Is there a perceived conflict of interest? I think as individuals are examined for their "revolving door", a bit too much at times has been made of this. Since people do have to leave the government at times, either of their own will or not of their own will, and need to find a job outside, it is not infrequent that they will take employment in industry—that is, one major sector of our economy. As long as the individual does not participate directly in any of these actions and has neither a real or perceived conflict of interest, that, I think, is an appropriate way to go.

What is perception? In effect, that is in the eye of the beholder, and that is why I was pleased to see the GAO account that really tried to focus on this. We need objective analysis. It is hard for an individual to give an opinion. I have tried to give an array of where individuals went, those ten that you mentioned.

Senator METZENBAUM. Senator Hatch?

Senator HATCH. Thank you, Senator Metzenbaum.

I have some questions for you, Dr. Young, but let me make a few comments.

First, Mr. Chairman, you have made some allegations regarding former FDA officials, so I ask that the record remain open so that they have an opportunity to respond to any of the issues that have been raised.

Commissioner YOUNG. And I will be happy to provide that for the record.

Senator HATCH. Yes, I think it is important.

Commissioner YOUNG. I did not see, as I looked at that, any actual conflict of interest, but as I said, Senator, the GAO focused on that as well, and did not find any conflict of interest.

Senator HATCH. Yes. How many people work at FDA?

Commissioner YOUNG. About 7,000. Turnover in the drug area, at least, is 10 percent per year.

Senator HATCH. My experience is that at FDA, they make less than they could make in comparable jobs on the outside, working in research facilities that are really not as adequate as they should be.

Commissioner YOUNG. That is absolutely correct.

Senator HATCH. And you have a dedicated group of scientists there who really believe in what they are doing. They put up with these conditions because we are not helping them have the state of the art scientific laboratories that they need—even though they certainly do a terrific job under the circumstances.

Let me just say this. Today's hearings are very important. We have had a number of them in the past, and this is the fifth day of hearings concerning the food additive, aspartame.

During the past decade, critics of this product have received much public and Congressional attention, with claims of adverse health effects believed to be caused by aspartame.

In the past, the hearings and the debate have centered on the process the Food and Drug Administration used in approving this food additive as safe for consumption, and on several highly-publicized scientific theories, both favorable and derogatory to aspartame.

Aspartame was first approved as a safe and effective substance for certain food additives in 1974. Since that time, aspartame has undergone rigorous scrutiny by FDA and others who have conducted 168 medical and scientific tests. In fact, FDA has subsequently approved the use of aspartame, as I understand it, for nine various uses. Is that correct?

Commissioner YOUNG. Yes.

Senator HATCH. At the same time, several Congressional hearings and investigations have been conducted on claims of ill health effects related to aspartame consumption or alleged manipulation of research data that supports aspartame. And most recently, the GAO completed an investigation that found, despite charges that FDA and others had doctored the science, that FDA has followed its required process in approving aspartame and monitoring adverse reactions in ongoing aspartame research.

Now, today, the key question we have focused on is the most important: Is aspartame safe? As we revisit the issue, I hope we in Congress will rely on the scientific experts, including those at FDA, to continue their efforts to scrutinize substances used in foods. If a product has a reasonable certainty of no harm, then Congress has authorized the Food and Drug Administration to approve its use in America's food supply. There is no food or drug in this society which is completely safe for every individual. People need to know that. There is no food or drug in this society that is totally safe for every individual.

Commissioner YOUNG. That is absolutely correct.

Senator HATCH. That is true. We cannot guarantee complete freedom from some adverse reaction or consumer complaint to products in our environment. And we do not live in a totally risk-free society; yet we have to do our best, based on sound scientific facts, to protect our citizens from serious harms that we can control.

After a detailed review of the scientific literature, the Food and Drug Administration, as I understand it, has concluded that aspartame is safe for the general population. And today, aspartame is the leading sweetener used in low-calorie foods and beverages in this country.

Now, Senator Metzenbaum states that he has found new evidence that he believes raises questions of aspartame's safety. He will be supported in that claim by several eminent scientists. Other scientists of equal reputation will dispute those claims as unfounded old claims. Now, I will be interested, as I am sure all of us will be, in the outcome of this byplay of ideas.

Today's hearing may also raise concerns about the integrity of today's system of industry funding of research on food products. Without specific evidence of wrongdoing, the mere taking of industry money does not impugn the integrity or reputation of the research or undermine the validity of the research. This is the way research funds are obtained in many instances, and research must go through peer review, the highest standards of scientific methodology, and designed to achieve scientific accountability. Beyond that, these studies must pass muster at the FDA.

If biased studies are escaping the scrutiny of peer review and the FDA, then we ought to exclude those studies. But aspartame's critics do the research community a considerable disservice to generalize, as they do about the FDA and industry being in cahoots, without being able to identify a single credible example of abuse of the process—not one.

Now, I want to add one bit of caution to today's hearings. And I might just say on that idea that my experience with FDA is, if there is a more highly credible, ethically functioning unit of Government than FDA, I would like to know what it is. You know that you are going to get killed if you make a mistake or if there is any kind of abuse of the process. Sure, we have our problems with some employees at FDA, just like everywhere else, who get upset or delay something by putting it on the bottom of the pile. But the fact of the matter is, I do not know of an agency with higher ethical standards that would exceed those of the FDA.

Commissioner YOUNG. Thank you. I have found that, coming in from the university just three and a half years ago. I have been impressed with the quality of staff in the agency.

Senator HATCH. So am I. That does not mean mistakes are not made, but I will be honest with you, I do not know of anybody who rises to the dignity of the ethical standards and high scientific review that FDA does.

Now let me add one word of caution to today's hearing. If I may, I would like to quote from Dr. William Pardridge, a leading critic of aspartame, who will be testifying here today. He said: "I am concerned with the widespread misinterpretation of my research by the media and the resultant public anxiety."

Now, I believe this summarizes the way we should treat this hearing, as an open debate on Congress 'role in the approval of food additives. This hearing should not become a media circus, frightening people unnecessarily and causing concern about our Nation's food supply or the safety of that supply. Today, both critics and proponents of aspartame will testify.

Now, Dr. Young, you have first witness, and I do not know of anybody who I admire more in Government than you. I think you have done a terrific job since you have been at FDA. It has been unbiased and it has been bipartisan. And as far as I can see, it is the way it should be done.

In addition I would like to submit for the record the views of several scientific and health organizations—the American Medical Association, the American Academy of Pediatrics, the Juvenile Diabetes Foundation, the Epilepsy Foundation, the Institute for Food Technologists, and the Epilepsy Institute all have reviewed the scientific data on aspartame and have affirmed the safety of the sweetener.

Now, the American Dietetic Association also recently approved a position statement indicating that the moderate use of sweeteners, including aspartame, is acceptable. They have requested that statements by them be included in the hearing record, so I hope you will do that, Mr. Chairman.

Senator **Metzenbaum**. Without objection.

[Information supplied follows:]

POSITION STATEMENT OF THE INSTITUTE OF FOOD TECHNOLOGISTS

IFT's Expert Panel on Food Safety and Nutrition, which studies significant food-related issues and oversees timely publication of Scientific Status Summaries, comprises twelve academicians representing expertise in one or more areas of food science/technology and nutrition. The Expert Panel, which changes annually due to three year term rotation, presently includes faculty of: The University of Arizona; The University of British Columbia; The University of California-Davis; Cornell University; The University of Florida; The University of Illinois; The University of Massachusetts/Amherst; The University of Nebraska; North Carolina State University; Rutgers University; The University of Wisconsin.

Sweeteners: Nutritive and Non-Nutritive

Scientific Status Summary by the
Institute of Food Technologists Expert Panel
on Food Safety & Nutrition

☐ Sweeteners have been used since prehistoric times, following the discovery of honey. Drawings in Egyptian tombs as early as 2600 B.C. illustrated bee-keeping practices for honey production, although the honey was probably reserved for the rich and powerful.

The earliest reference to sugar and sugar cane occurred in a scroll from 375 A.D. The Arabs developed the first refining processes by the 14th century A.D. The sugar refining process then spread through Europe and eventually to the New World. A method of making syrup from the sap of the sugar maple tree was devised by North American Indians long before the Pilgrims arrived in Massachusetts and sucrose was isolated from a root-crop (beets) before the 18th century.

Research has shown that people have an inborn desire for sweet taste. Furthermore, the response to sweet solutions has been shown to be an innate reflex reaction, rather than a reaction acquired by conditioning or learning.

Today, sweeteners of one kind or another are found in the diets of most, if not all, individuals. A sweetener may be in the form of granulated sugar added to food at the table or it may be in the form of other sweeteners such as syrup or honey. It may even be a manmade substance such as saccharin or aspartame, contributing few if any calories to the foods it sweetens.

Each of these sweeteners and the others which are available to us, however, has specific applications and certain limitations. Therefore, a large variety of sweeteners exists as a result of our individual dietary needs and our demands for high-quality, good-tasting food.

NUTRITIVE SWEETENERS

Any sweetener which provides calories, or food energy, is considered a nutritive sweetener. Sugars, syrups, molasses, sugar alcohols, and honey are therefore all classified as nutritive sweeteners. Each provides approximately the same number of calories, gram for gram. Aspartame is categorized as a nutritive sweetener by the U.S. Food and Drug Administration (FDA), because it contributes the same number of calories per gram as sugar. Aspartame however, can be used in very small quantities because it is approximately 200 times sweeter than sucrose. Therefore, aspartame's calorie contribution to the foods it sweetens is insignificant.

Sugars

Sugars (saccharides) are the most commonly recognized of the nutritive sweeteners. They are widespread in nature, occurring in fruits, vegetables, honey, and milk. Sugars are the "building blocks" of more complex carbohydrates (polysaccharides) such as starch, cellulose, pectin and glycogen ("animal starch"). They also appear in many simple and complex organic molecules, including DNA, the backbone of genetic material. These polymeric compounds are not sweet, but are caloric. All carbohydrates must be broken down into molecules of "simple sugars" (monosaccharides) before they can be utilized in the body. Glucose and fructose are the most common monosaccharides.

Also known as dextrose, glucose is the main form into which other sugars and carbohydrates are converted in the body, and thus is the main sugar found in human blood. Glucose is naturally present in many fruits and is the basic "repeating" unit of starches (found in most plant foods) and of glycogen, the starch found in animal muscle tissue.

Fructose (levulose or fruit sugar) is the sweetest of all the natural sugars (up to one-and-a-half times as sweet as sucrose) and is generally found in foods such as fruits and honey. For example, an apple is about four percent sucrose by weight, six percent fructose, and one percent glucose, whereas a grape is about two percent sucrose, eight percent fructose, seven percent glucose, and two percent maltose (Shallenberger, 1974).

Sucrose is the common sugar for household and industrial use. It is the most abundant sugar found in the plant kingdom and has been used since antiquity (Meade and Chen, 1977). Sucrose is a disaccharide composed of two simple sugars—glucose and fructose, chemically attached together. Table sugar is about 99.9 percent pure sucrose, and is produced by concentrating sucrose from sugar cane or sugar beet juice. The crystals that form are then purified and separated from the remaining organic matter and various minerals. Sucrose is of major importance because of its acceptability and palatability, along with its ready availability, general low cost, simplicity of production, purity and long history of use (Inglett, 1981). Traditionally, the word sugar has been used to mean sucrose, but this can be confusing since there are other sugars.

Raw sugar is an intermediate product of sucrose production.

Dr. Rosetta L. Newsome, IFT Office of Scientific Public Affairs' science associate, was the principal editor of this Scientific Status Summary

The raw sugar crystals are covered with a film of syrup which contains impurities. During processing, a dark-colored liquid is produced, as a result of chemical interactions which occur in the solution at high temperatures. This liquid, molasses, was commonly used in the 1700's and 1800's as a sweetener as well as a fermentation food for yeast in making rum. Molasses syrup contains 50 to 75 percent sucrose. Blackstrap molasses is a byproduct of the final molasses crystallization step. This bitter product is primarily used in cattle feed and for industrial purposes.

Lactose is a disaccharide composed of the two simple sugars, glucose and galactose, chemically bound together. Human milk contains about 7.5 percent lactose while cow's milk contains about 4.9 percent (Shallenberger, 1974). Lactose is normally degraded in the intestine by the enzyme lactase into its two component sugars. However, some children and adults have low lactase levels. In these lactase deficient individuals, undigested lactose goes into the lower intestine and is fermented by bacteria there, resulting in abdominal distention, flatulence, and in some cases, watery stools (Gray, 1980). Although the deficiency may be inherited, it is manifested more frequently in adulthood because intestinal lactase activity naturally decreases with age (Sandine and Daly, 1979). Lactose intolerance is more common in North American blacks, Africans, and Asians than in North American Caucasians (Cuatrecasas et al., 1965; Gray, 1980; Huang and Bayless, 1968).

Maltose, or malt sugar, is obtained from the fermentation of starches by enzymes or yeast. Starches, as noted above, consist of chains of glucose. Maltase enzymes produced by yeast degrade starch into a sugar comprised of two glucose molecules, i.e., maltose. Maltose also is created during breadmaking as a result of starch degradation by enzymes present in the flour. Commercially, maltose may be produced by partial acid hydrolysis of starch. Barley malt, in which barley starch is similarly fermented, is used as an adjunct in brewing, enhancing the flavor and color of beer as a result of the maltose content.

Honey is a natural syrup made from plants by honeybees. It may vary in composition and flavor depending on the plant source from which the nectar was collected, the amount of processing, and the length of storage. Since a variety of plants naturally produce toxic components, honey may also contain toxic materials (Patwardhan and White, 1974). The principal sugars contained in honey are fructose and glucose, the same components in table sugar. Although honey contains minute amounts of vitamins and minerals, the contribution of these essential nutrients to the diet is insignificant.

Maple syrup is derived from the spring flow of the sap of mature sugar maples *(Acer saccharum)*. It is composed almost entirely of sucrose. The syrup is used for flavor as well as for sweetness. Maple sugar may be produced by boiling off the liquid from the syrup.

Corn Syrup

First developed in the 1920's, this sweetener is derived from corn starch by treatment of a starch slurry with acids, heat, and/or enzymes. It is composed of molecules of different glucose chain lengths. These syrups are not as sweet as sucrose but are very often used in conjunction with sugar in confections, ice cream and other food products because of their texturizing properties. Corn syrups have proven to be an effective replacement for sucrose in the brewing, canning, baking, and pet food industries because they are less sweet than sucrose but give "body" and thus higher viscosity to the product.

High-Fructose Corn Syrup (HFCS)

High-fructose corn syrup is made by a unique enzymatic process which converts glucose, derived from corn starch, to fructose. This process, which uses the immobilized enzyme glucose isomerase, was developed in 1970 and is a good example of the use of biotechnology. High-fructose corn syrup may be made with a composition of from 40 to almost 100 percent fructose. Since fructose has a higher perceived sweetness than sucrose, use of HFCS (with high levels of fructose, i.e. 90 percent) in food products allows a reduction in the quantity of sweetener used and allows for a lower calorie product. High-fructose corn syrup is used in many food and beverage products and is the main nutritive sweetener used in the soft drink industry.

Sugar Alcohols

Also known as polyhydric alcohols or polyols, sugar alcohols are sweetener substitutes which, except for xylitol, occur naturally, in fruits. Sugar alcohols are important in some foods for their texturizing properties. Common applications include chewing gum, hard candies, and coatings on tablets and gums.

In addition, some sugar alcohols have other useful properties. For example, although it contains the same number of calories per gram as other sweeteners, sorbitol is absorbed more slowly from the digestive tract than sucrose (Wick et al., 1951). It is, therefore, useful in making foods intended for special diets. Sugar alcohols are especially common in dietetic candy and chewing gum because they do not promote tooth decay. Sorbitol, mannitol, and maltitol are considerably less sweet than sucrose, while xylitol has about the same sweetness. When consumed in large quantities, however (25 to 50 grams or one to two ounces per day), sorbitol can have a laxative effect, apparently because of its slow intestinal absorption (Ellis and Krantz, 1943; Peters and Loch, 1958). This laxative effect may be particularly encountered among small children who swallow dietetic chewing gum.

Xylitol is a normal intermediate product of carbohydrate metabolism in man and animals, and it occurs naturally in a wide variety of fruits and vegetables (Emodi, 1978). It is obtained from xylan found in wood pulp, chips, nutshells, cane sugar bagasse, straw, or corncobs.

With regard to the safety of xylitol, the Code of Federal Regulations states that it "may be safely used in foods for special dietary uses, provided the amount used is not greater than that required to produce its intended effect" (21 CFR 172.395).

A new polyol, Lycasin®, has been developed by Roquette Frere Laboratories (New York, N.Y.) by hydrogenation of corn syrup. Lycasin is only one-fourth to one-half as sweet as sucrose, but does not promote tooth decay and is less likely to produce diarrhea than the other polyols (Anonymous, 1986). The FDA has not yet acted upon the petition for GRAS status (June, 1986).

Aspartame

Commonly known by the trade name NutraSweet®, aspartame was discovered in 1965 by a scientist at G.D. Searle and Company (Skokie, Ill.). Chemically, the compound is a methyl ester of two amino acids, phenylalanine and aspartic acid (aspartate), which are both naturally found in food. Aspartame is therefore digested in the same manner as other amino acids and peptides. Because aspartame contains phenylalanine, products which contain it must be labelled to notify individuals with phenylketonuria (a rare inherited disease which requires control of dietary intake of phenylalanine) that it is present in the product. The label must state "Phenylketonurics: contains phenylalanine."

Although it is a nutritive sweetener because it is calorically equivalent to sucrose, aspartame's sweeteness is very intense (180 to 220 times sweeter than sucrose), and therefore only a small amount is needed to sweeten products. Aspartame's taste is very similar to sucrose, and it does not have an aftertaste. It enhances some flavors, and in combination with saccharin it results in a sweeter taste than either one has alone. At high temperatures, aspartame undergoes a reaction which causes a loss of flavor, thus it is not used in canned foods or in products which are baked or roasted. Cooking and baking recipes usually carry a notice that aspartame may not be effective under the prescribed conditions. Aspartame can be used in acidified liquids and high acid carbonated beverages but will also degrade and lose flavor in more neutral solutions such as dairy-based drinks. It is approved for use as a free flowing sugar substitute or tablet form for table use, as a dry base sweetener for powdered beverages, desserts, dessert toppings, carbonated beverages, and as a flavoring agent in chewing gum in the U.S., Canada, and 22 other nations.

Regulatory History. Aspartame was first approved in 1974 (21 CFR 172.804) but the approval was subsequently stayed. In addition, formal objections based on possible toxic effects of aspartame's constituent amino acids when fed in high amounts to animals, were received from two sources. Following a lengthy legal hearing by a court appointed scientific board of inquiry and a scientific audit of the authenticity of the toxicological studies (which had been questioned), FDA concluded that aspartame was safe, and the stay of the original regulation was withdrawn in October 1981. The FDA asked the manufacturer to monitor the subsequent actual use levels of aspartame and provide this information to FDA upon request. Aspartame was also approved in Canada in 1981 for use in a variety of food products, as a table-top sweetener, as well as for use in carbonated beverages.

In determining the safety of aspartame, several estimates of aspartame consumption levels were made (FDA, 1981). The level of consumption was projected to be less than 34 mg/kg body weight/day for 99 percent of the population. From this, the acceptable daily intake was set at 50 mg/kg body weight/day. This level included projected use of the sweetener in soft drinks, although use of aspartame for this purpose was not being petitioned for at that time.

In July 1983 FDA approved a subsequent petition for aspartame use in carbonated beverages and the syrups used for carbonated beverages (48 FR 31376). Objectives to this approval were filed, alleging various possible safety concerns and a stay of the approval was requested. After careful review of the specific safety issues raised in the objection, the Commissioner of FDA declined the stay stating that "the objections do not provide evidence that potential harm to public health may result from the use of aspartame in carbonated beverages and therefore the safety issues raised in the objections do not warrant a stay of the approval" (48 FR 52901). FDA further reported that "the physiological and neurological effects of aspartame have been comprehensively studied over the previous ten years and that most of the issues raised in the objections were substantially identical to issues that it had already examined and resolved in its prior determination of aspartame's safety." In approving aspartame for use as a food additive, the FDA Commissioner added that "few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety" (46 FR 38289).

Since the approval of aspartame, various parties under the law have requested that FDA conduct public hearings concerning its use in dry foods as well as in carbonated beverages, but each petition has been denied by FDA because, among other factors, critics have failed to present any new evidence that it is unsafe.

Safety Aspects. The various objections to aspartame's approval which have been raised concern one or more of its metabolites: phenylalanine, aspartic acid, methanol, and diketopiperazine (DKP). Literature concerning aspartame's safety is exhaustive. More than one-hundred studies have analyzed the various effects that these metabolites might have following consumption of normal (no greater than the 99th percentile projected level of consumption, i.e. 34 mg/kg/day) and abnormally high levels of aspartame. Except for DKP, these metabolites are naturally present in foods or they form during cooking or processing. Phenylalanine and aspartic acid enter normal cellular function, while methanol is detoxified and excreted as formate. These compounds are safe when consumed in normal amounts, but as with any substance, they can have adverse health effects if present in the body in very large amounts.

Aspartate. Aspartic acid can be interconverted into the amino acid glutamate in the body. Because very high levels of either one of these amino acids may cause central nervous system damage, research was conducted to determine the effect of aspartame on the blood levels of aspartate and glutamate. Results of studies on adults as well as children have shown that consumption of normal and abnormal levels of aspartame did not result in elevated blood levels of these amino acids (Filer et al., 1983; Frey, 1976; Stegink et al., 1977). Since glutamate occurs in the food additive monosodium glutamate (MSG) as well as in protein containing foods, studies of aspartame added to foods containing MSG and to foods containing MSG with additional protein were conducted (Reynolds et al., 1980; Stegink et al., 1982; Stegink et al., 1983a). Significant elevations in blood levels of these amino acids did not occur even when aspartame was administered in high doses. Changes observed in the amino acid levels were similar to changes following consumption of a normal meal.

Phenylalanine. In individuals with the inherited disease phenylketonuria (PKU), the essential amino acid, phenylalanine, is not metabolized properly. Instead, it builds up to high concentrations in the blood as a result of a lack of the enzyme necessary to metabolize the amino acid and, secondarily, increases in concentration in the brain. Sustained high phenylalanine concentrations in individuals with PKU can cause brain damage.

Aspartame administered in a large dose (200 mg/kg) caused increases in brain and plasma levels of phenylalanine in rats (Fernstrom et al., 1983; Yokogoshi et al., 1984). However, studies designed to determine the effects in humans have shown that when ingested in normal or excessive (up to 200 mg aspartame/kg) amounts, even when administered as a single dose, aspartame did not cause an abnormal or unusual rise in blood phenylalanine (Stegink et al., 1977). Extensive research has shown that consumption of aspartame is safe for normal adults and children, normal pregnant women, their unborn children, lactating women and their nursing infants, and persons with diabetes (Bauer-Nehrling et al., 1983; Filer et al., 1983; Frey, 1976; Koch et al., 1976; Stegink et al., 1979; Stegink et al., 1980; Stegink et al., 1981a; Stern et al., 1976). FDA concluded that the data establish that there is a reasonable certainty that the proposed use of aspartame will not cause or aggravate the type of brain damage associated with sustained high plasma levels of phenylalanine (46 FR 38291).

Other questions have been raised concerning the effect of elevated blood and brain phenylalanine concentrations on other amino acids, and the resultant effects on behavior. The amino acids of interest are those which the brain uses to synthesize neurotransmitters (chemicals which influence brain activity). Changes in neurotransmitter concentrations affect brain function and thus mood and behavior. A considerable amount of research has shown that aspartame, as well as phenylalanine, administered to animals in normal to extremely high levels, did not cause substantial changes in neurotransmitter levels, behavior, brain wave abnormalities, seizures, or in physical or mental development (Brunner et al., 1979; Ishii, 1981; Potts et al., 1980; Reynolds et al., 1984; Suomi, 1984).

Furthermore, studies in which aspartame was administered to humans (adults and infants) in single doses of 34 to 200 mg/kg or 1800 mg/kg aspartame per day for 21 weeks failed to show any clinically detectable changes in behavior. Fernstrom et al. (1983) however, observed changes in brain amino acid concentrations in rats fed large doses of aspartame, but found no changes in neurotransmitter levels. Wurtman (1985) cited three incidences in which people with no previous history of epilepsy experienced seizures after consuming large amounts (five glasses to more than seven and one-half liters of aspartame-sweetened beverages per day) of aspartame. He stated that phenylalanine inhibits the synthesis of monoamines, a lack of which has been associated with grand mal seizures. A more recent article reported some localized changes in neurotransmitter concentrations in rats, but the human health implications remain unclear (Coulombe and Sharma, 1986). Research on this subject will undoubtedly continue in the future.

Methanol. Another concern is the question of the degradation of aspartame to methanol, either in carbonated beverages before consumption or in the gastrointestinal tract after consumption. Methanol (in the methyl ester form) constitutes approximately ten percent of aspartame by weight. This means, that if all the aspartame in a twelve-ounce diet beverage were degraded, there would be about 21 mg methanol present. Methanol may be degraded in the liquid before consumption or in the body afterwards. Only excessive methanol intake can result in toxic levels sufficient to cause methanol poisoning (metabolic acidosis and ocular damage).

Methanol occurs naturally in the diet, in fruit juices, baked potatoes, and alcoholic beverages (in which case it may occur in larger concentrations than in aspartame). Methanol is thus a normal metabolite of digestion in the human body. In the body, methanol is metabolized to formaldehyde, which is then rapidly degraded to formate. A toxic level of formate is the responsible factor in methanol poisoning. Studies conducted in adults and children have shown that when administered at levels similar to that of a heavy user, aspartame caused no changes in blood methanol or formate levels (Stegink et al., 1983b). Blood formate levels and urine excretion of formate were studied in adults which were administered a single dose of 200 mg/kg (six times the 99th percentile of estimated intake), equivalent to consumption of more than 50 twelve ounce cans of aspartame sweetened beverage at one time (Stegink et al., 1981b). The subjects showed no increase in blood formate levels and sufficiently rapid excretion of formate. These levels were well below the level of toxicity. Infants given 100 mg/kg aspartame per day showed methanol levels similar to those in adults, indicating similar rates of metabolism and excretion. FDA reported that it found no cause for concern with the levels of dietary methanol resulting from the highest levels of aspartame consumption (48 FR 31376 at 31380).

Diketopiperazine. DKP is an intermediary metabolite of aspartame which may occur in products following prolonged heating or lengthy storage at high temperatures. Upon formation it is further degraded to the individual amino acids phenylalanine and aspartate, in both the liquid in which it is formed and in the human body. This particular compound is not a common food ingredient. It has thus been subjected to safety testing in animals to determine any possible chronic, carcinogenic, reproductive or mutagenic effects. None of the studies of DKP revealed formation of harmful substances or any direct deleterious health effects (Bryan, 1984; FDA, 1983; Ishii et al., 1981). Thus, aspartame containing products exposed to excessively high temperatures as a result of boiling or temperature abuse will exhibit at most, a loss in sweetness intensity.

Carcinogenicity. Aspartame has undergone extensive cancer studies just as any new food additive has. The molecular structure of aspartame is such that it is rapidly converted in the body to metabolites which would not

Table 1—**Other Nutritive Sweeteners***

Name	Source	Applications	Status
Glycyrrhizin or Glycyrrhizic acid	Licorice plant (*Glycyrrhiza glabra* L.) roots from Europe and Central Asia	Flavoring agent in pipe, cigarette and chewing tobaccos, confectionery manufacture, medicines, root beer, chocolate, vanilla, liquers; in Japan, in hydrolyzed vegetable protein, soy sauce, and bean paste	U.S.: GRAS flavoring agent
Talin®, thaumatin I or II	Fruit of W. African *Thaumatoccus danielli*	Flavor potentiator and extender in chewing gum, toothpaste, mouthwash, and other pharmaceuticals and cosmetic products	England: marketed by Tate and Lyle, Ltd. Approved for use in Japan (1979), U.K. (1983), Mexico, and in Australia as a flavor enhancer (except in baby food) (1984) U.S.: GRAS flavor adjunct in chewing gum (GRAS list XIII, publ. in *Food Technology*, October 1984). No other use is allowed.
Monellin	W. African serendipity berry *(Discoreophyllum cumminsii)*	Instability precludes commercial development at this time	Developmental stage at Monell Chemical Senses Center, Philadelpha, Pennsylvania
Stevioside	Leaves of *Stevia rebaudiana* in Paraquay	Sweeten bitter drinks in Paraquay; many common uses in Japan	Japan: Approved U.S.: Not Approved
Miraculin	Berry of W. African miracle fruite *Richardella dulcifies*	Flavor modifier to sweeten sour fruits, vegetables, yogurt	U.S.: GRAS status denied Others: Introduced into Jamaica, Puerto Rico, Brazil, and Panama by the Miraculin Corp. (no longer in existence)

*Except for glycyrrhizin, these intense sweeteners, or flavor enhancers, are common in other countries but not in the U.S.

present a carcinogenic hazard. Animal studies have not revealed any carcinogenic effects of aspartame. Although the adequacy of two initial cancer studies was debated, the issue was resolved and it was finally agreed that additional studies were not needed (FDA, 1981).

Consumer Complaints. Questions in the media about aspartame's safety have also focused on a variety of consumer complaints. Symptoms such as nausea, dizziness, mood changes, headaches, epileptic-like seizures, and menstrual irregularities have been reported. Evidence of this type is often regarded as anecdotal since the incidences are varied individual reactions which have not been observed in controlled studies. Additionally, most of the complaints were received after widespread newspaper and TV coverage of questions raised by critics.

Reports of this nature, by individuals attempting to associate a product with unexplainable physical symptoms, are expected upon introduction of a new food product, particularly one which has received substantial media coverage. An investigation of more than 500 consumer complaints by the Center for Disease Control (Atlanta, GA) did not clearly link any symptoms to the use of aspartame (CDC, 1984). CDC reported that the reactions were diverse, revealing no consistent patterns.

Dr. Richard J. Wurtman of Massachusetts Institute of Technology recently submitted to FDA case summaries of 35 patients who suffered seizures allegedly related to aspartame consumption and met with FDA to discuss the cases (*Food Chemical News*, April 21, 1986, p. 65). Kulczycki (1985) recently reported allergic reactions to aspartame which had not been previously documented. The reactions—which included hives, itching, rashes, and swelling—were experienced by one woman. The adverse reactions were confirmed by rechallenging the patient with 25 and 75 mg aspartame, followed by controlled observation (Kulczycki, 1985). On March 18, 1986, The Epilepsy Institute released to the press the statement that the organization had found aspartame to be safe for people with epilepsy. The Chairman of the Professional Advisory Board for the Epilepsy Institute stated that he had received the data and saw no cause to link aspartame to seizures. Further, he stated, "At the Epilepsy Institute, where there are 5,000 client visits a year, there have been no reports of change in seizure patterns."

FDA has recently formed a special Food Program for monitoring the situation to detect adverse reactions. The FDA is also investigating additional exposure data for children between the ages of two and five years, as a result of reports that this particular age group may be consuming more aspartame than the estimated acceptable daily intake. At this time, there is no scientific evidence to dispute aspartame's public health safety. An FDA Ad Hoc Committee on Hypersensitivity to Food Constituents recently concluded that no evidence exists that aspartame or its breakdown products are significant health hazards in their current use but that further research is needed since the information currently available is inadequate.

Other Sweeteners

A number of other sweeteners of natural origin are used to sweeten foods in other countries. Most of these come from plants which do not grow in the U.S. These substances, listed in Table 1, usually are derivatives of naturally occurring sugars or proteins. These sweeteners are intensely sweet substances which can be used in very small quantities, thus they contribute few if any calories to the foods and beverages they sweeten. Some of them have been approved for use by the FDA but are very seldom used because of instability or the presence of other flavors.

Why are Nutritive Sweeteners Added to Foods?

Most of the uses for sugars and other sweeteners in food processing are similar to uses in the home, i.e., nutritive sweeteners are used in food products principally for their sweetening power. In addition to satisfying the natural human desire for sweet tasting foods, sweeteners make other foods more palatable. Sprinkled on grapefruit, for example, they take away the sour taste; stirred into chocolate, they offset the bitterness.

Sugars have several other properties which are important both to industry and home use. One is the preservative effect, which is vital to the keeping quality of products such as jams, jellies, syrups, and candies. Sugars have the ability to bind water. This makes water less available and reduces the growth of microorganisms. Thus, sugars aid in prevention of spoilage. The binding property is described by the term "water activity" by food scientists. Sweeteners add to the preservative effect in cured meats, as well as enhancement of their flavor.

Sugars may serve as food for yeasts and other fermenting microorganisms in the manufacture of bread, pickles, and alcoholic beverages. These sugars are metabolized in the fermentation process and are not present in the finished product, unless they are added for sweetness after fermentation. Sweeteners also contribute to crust color and flavor in baked goods.

Sugars provide body, bulk (or "mouthfeel") and texture as in syrups, candies, and baked goods. Mixtures of sweeteners can provide functional advantages such as control of freezing point, crystallization in ice cream, and control of spoilage in products such as jams and jellies. Small amounts can be used with non-nutritive sweeteners such as saccharin to mask the bitter aftertaste and to provide bulk.

The versatility of various sweeteners makes them indispensable ingredients in many of our foods.

Sweeteners and Dental Caries

It is well known that sugars and carbohydrate foods contribute to tooth decay in susceptible individuals. In order for a cavity to form however, three things are necessary: bacterial plaque on the surface of a tooth, a susceptible tooth, and a fermentable carbohydrate (Anonymous, 1976; Mandel, 1981). Dental caries is a result of bacterial growth on the tooth surface, metabolism of fermentable carbohydrates in the mouth by these bacteria and the subsequent formation of acid. Fermentable carbohydrates include both simple and complex sugars as well as starches. These include the sugars and starches found in candy, honey, apples, milk, raisins, bread, and many other foods. Any food that will produce acid in the mouth can be cariogenic. Studies have shown that corn syrups (high fructose as well as glucose and fructose mixtures) are cariogenic (Bowen, 1984; Colman et al., 1977). Little practical dental benefit would be derived by substitution of these sweeteners for sucrose. Dental caries is a result of bacterial growth on the tooth surface, metabolism of sugars in the mouth by these bacteria and the subsequent formation of acid.

Studies have indicated that saccharin and aspartame are noncariogenic and that they may be anti-cariogenic as well. Saccharin inhibits growth of plaque-forming bacteria through inhibition of their enzyme production (Linke, 1977; Linke and Kohn, 1984). Also, aspartame has been shown to neutralize the acidic conditions created during plaque formation (Mishiro and Kaneho, 1977). The cariogenic effects of other less common sweeteners has not been determined. However, any noncarbohydrate substance which can be used in low concentrations is unlikely to be cariogenic (Bowen, 1984).

Sugar alcohols are advantageous because of their relatively low cariogenic potential. Studies have shown that there is approximately a 30 percent reduction in dental caries in rats fed sorbitol and mannitol containing diets, and virtually complete elimination of caries in rats fed a xylitol containing diet, compared with cariogenic diets (Bowen, 1978; Grundberg, et al., 1973). Other studies conducted in humans and animals indicated that xylitol may inhibit dental caries (Bird et al., 1977; Leach and Green, 1981; Makinen et al., 1978).

While many studies link sugar consumption to cavities, scientists believe that the number of dental cavities a person actually develops depends more on the frequency of consumption than on the total amount of food consumed (Bowen, 1978; Edgar et al., 1982). Sugar eaten between meals is more cariogenic than that consumed with meals. In addition, the incidence of tooth decay is influenced by:

1. The level of fluoride in drinking water and foods, and the use of dental products;
2. the form in which sugar is eaten ("retentiveness");
3. the other ingredients in the sugar-containing food;
4. the length of time sugar is in contact with the teeth;
5. genetic susceptibility of the individual to dental cavities;
6. the flow and composition of the saliva; and,
7. other undefined dietary factors.

Table 2—**Other Non-nutritive Sweeteners**

Name	Source	Applications*	Status
Neohesperidin	Derivative of dihydrochalcones from citrus products (particularly grapefruit)	Chewing gum, confections, mouthwash, toothpaste, some fruit juices, and pharmaceuticals	Petition for GRAS status denied, insufficient toxicological testing. National Toxicology Program conducting research.
Acesulfame K	Derivative of acetoacetic acid	Hot and cold beverages, baked goods, milk products, table-top sweeteners, animal feed, cosmetic, and pharmaceutical products.	Approval petitioned by American branch of Hoechst AG, West Germany. Approved for use in the United Kingdom, Ireland, Germany, Belgium, and Australia
L-Sugars	Stereoisomer of naturally occurring "right-handed" or D-Sugars	In addition to similar products for D-Sugars, potential applications include low-calorie products due to its inability to be metabolized	Patent granted to Dr. Gilbert Levin, Biospherics, Inc., Rockville, Maryland
Neosugar	Derivative of sucrose produced by fungal enzyme fructosyltransferase	Low-calorie products due to its inability to be metabolized	Developmental stages in Japan.
Trichlorogalacto-sucrose (TGS Sugar)	Derivative of sucrose produced by chlorine substitution of hydroxyl groups	Low-calorie products due to its inability to be metabolized and in heat processed foods due to its thermal stability	Petition for approval expected in 1986; from Johnson and Johnson, Inc., New Jersey In developmental stages at Tage & Lyle Ltd. (England)

*These sweeteners are not yet approved for use in the U.S.; therefore, their applications are only potential in this country.

Water fluoridation along with the use of fluoride products can decrease tooth decay by as much as two-thirds. Brushing teeth properly, flossing, placement of dental sealants, and minimization of between meal snacks further decreases formation of cavities.

Other Diseases

Many conditions such as coronary heart disease, obesity, diabetes, hyperactivity, and hypoglycemia have frequently been associated with consumption of sucrose. However, a careful review of these theories by a blue-ribbon panel of the Federation of American Societies for Experimental Biology (FASEB, 1976) for the U.S. Food and Drug Administration concluded: "Other than the contribution made to dental caries, there is no clear evidence in the available information on sucrose that demonstrates a hazard to the public when used at the levels that are now current and in the manner now practiced." Subsequent experimental evidence has supported this conclusion (Bantle et al., 1983; Behar et al., 1984).

For those who wish to lose weight, some form of caloric restriction and/or increased calorie expenditure is necessary. This is especially true for those people who may eat too much of certain foods solely because of their sweet taste. Obesity is one of many risk factors which have been linked to a number of diseases including coronary heart disease and cancer.

NON-NUTRITIVE SWEETENERS

Non-nutritive sweeteners are those sweeteners which are not metabolized by the body and therefore do not contribute any energy or calories to the diet. These sweeteners are especially advantageous for persons on diets requiring calorie restriction (persons with some types of diabetes and overweight persons) and for the prevention of dental caries. Currently, saccharin is the only non-nutritive synthetic sweetener allowed for use in the U.S., while in Canada, none of the non-nutritive sweeteners are approved for general food use except for some specific uses of cyclamate. Other non-nutritive sweeteners which are in various stages of development in the U.S., some of which are approved for use in other countries, are listed in Table 2.

Saccharin

Saccharin, discovered in 1879, is an organic petroleum compound which originally was used as a food preservative. Approximately 200 times sweeter than sucrose, it is absorbed slowly, but not metabolized and is rapidly excreted from the body, unaltered by the kidneys. Thus saccharin contributes no calories to the diet. Functionally, saccharin is stable within a wide range of temperatures and is colorless, odorless, and water soluble.

Regulatory History. Saccharin was the only non-nutritive sweetener available in the U.S. for many years. In the early 1900's, it was used particularly in over the counter drugs and in special dietary foods for the obese. After cyclamate was approved for various uses beginning in the 1950's, saccharin was used with it in a 10:1 cyclamate/saccharin combination, resulting in a greater sweetness than either substance alone. At this time the diet consciousness of the U. S. population increased dramatically and both began to be used in more foods, especially in diet beverages. After cyclamates were removed from the market in 1969, saccharin was the only synthetic sweetener available until aspartame was discovered and approved for use in 1981.

Saccharin was originally classified in 1958 as a "Generally Recognized as Safe" (GRAS) substance. Thus, saccharin was exempt from the Food Additives amendment to the FD&C Act which requires premarketing safety testing of food additives. GRAS substances are exempted on the basis of previous scientific testing or a history of safe use in foods. In 1972 saccharin was deleted from the GRAS list following a study by the Wisconsin Alumni Research Foundation (WARF) (Tisdel, 1974) which suggested, but did not clearly demonstrate, a link between saccharin and bladder cancer in rats.

Removal of saccharin from the GRAS list and its placement in an interim use additive status subjected it to the provisions of the FD&C Act and the Delaney Clause which states that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal." In 1977, following a study conducted by the Canadian Health Protection Branch which showed evidence of bladder tumors in second generation male rats fed high doses of saccharin (Arnold et al., 1980), FDA proposed to prohibit its use entirely, invoking both the Delaney Clause and the general safety clause which states "no such regulation shall issue if a fair evaluation of the data before the secretary: (A) Fails to establish that the proposed use of the food additive under the conditions of use to be specified in the regulation will be safe" (FD&C Act 409(3)(A)). Saccharin was banned in 1979 in Canada for general use, but was permitted for sale in pharmacies as a table-top sweetener.

As a result of public outcry against the proposed ban of its use in the U.S., the U.S. Congress passed the Saccharin Study and Labelling Act (1977), declaring a moratorium on the ban until additional research on its safety could be conducted. Further congressional action extended the moratorium in 1979, 1981 and 1983. The most recent moratorium extension went into effect June 30, 1985, extending it to 1987. The act and its extensions required more toxicological research and a warning label on all saccharin containing foods stating: "Use of this product may be hazardous to your health. This product contains saccharin which has been determined to cause cancer in laboratory animals."

Experimental and Epidemiological Data. Since the 1977 Canadian study, many experimental studies have been conducted to assess the potential effects of the long-term use of saccharin. Since impurities may contribute to the toxicity of a compound, studies of the impurities in commercial lots of saccharin were conducted. Impurities were observed in concentrations of less than 1 ppm, but they were identified as derivatives of the polyethylene storage bags (Riggin and Kinzer, 1983). A related study showed low-level mutagenic activity in extracts of commercial saccharin samples (Riggin et al., 1983), but the authors concluded that the saccharin contaminants were of little toxicological significance in animal feeding studies since very large amounts of the organic extracts were required to produce a mutagenic response.

The major contaminant of saccharin (ortho-toluenesulfonamide), which occurs as a result of the chemical manufacturing procedure, was shown not to cause cancer in rats (NRC/NAS, 1978). The Canadian study which prompted the saccharin ban was designed to study the contaminant, but scientists included saccharin in the study as well, fed as five percent of the diet (Arnold et al., 1980). This study indicated that the impurity did not cause an increase in bladder tumors in second-generation male rats, but that saccharin did. The dose given to the rats however, would be equivalent to several hundred cans of diet soft drinks per day for a human. Furthermore, to reproduce conditions similar to those in the experiment, one would need to be exposed to the saccharin in utero, throughout the entire lifespan, in order to consume an equivalent level.

The Committee for a Study on Saccharin and Food Safety Policy of the National Academy of Sciences reviewed fourteen single generation lifetime-feeding studies (NRC/NAS, 1978). Saccharin did not induce cancer in any organ in rats, mice, hamsters or monkeys. Other studies however, have suggested bladder tumor promotion in male rats (Cohen et al., 1979; Fukushima et al., 1983; Nakanishi et al., 1980; Nakanishi et al., 1982).

A 1983 study by the International Research and Development Corporation (IRDC) addressed the dose response question for bladder tumors in saccharin treated rats, along with other health questions. The study included a very large number of rats (2500 second generation males as opposed to approximately 300 animals of both sexes in a typical toxicity study) at several dose levels. It also included additional groups exposed to saccharin only, before birth or only after birth, in order to determine if prenatal exposure was critical. The study showed that high doses of saccharin produced significant physiological changes in rat bladder tissue and that exposure before birth was not necessary for tumor formation. Exposure during the nursing period, however, appeared to be necessary; the animals which were exposed to saccharin during gestation only did not develop bladder tumors. However, it should be noted that suckling rats are at a different developmental stage than humans.

The incidence of tumors in this study declined sharply with decreases in dose. The review panel concluded that tumor development in rats appeared to be a sex-specific, species-specific and organ-specific phenomenon. Based on the data in the IRDC study, mathematical models were then used to estimate the hypothetical increased risk of bladder cancer that could be caused by exposure to saccharin at ordinary human consumption levels. The models indicated that exposure to saccharin at a level of 0.01 percent of the diet (approximately two to three twelve ounce cans of saccharin-sweetened diet beverage per day) over a lifetime would increase the chance of developing bladder cancer by much less than one in one million (IRDC, 1983).

A considerable amount of epidemiological evidence supports saccharin's safety for humans. This evidence includes studies of disease patterns (particularly bladder cancer rates), patients with diabetes and case-control studies of patients with bladder cancer. Only one study did not support saccharin's safety (Howe et al., 1977) but it was widely criticized in the professional literature, including the journal in which it was published (Anonymous, 1977).

An extensive study conducted by the National Cancer Institute which involved 9,000 people revealed that in the total study group the use of artificial sweeteners was not associated with an increased risk of bladder cancer in either males or females (Hoover and Strasser, 1980). An association was seen, however, in two subgroups—white males who were heavy cigarette smokers and nonsmoking white females with no known exposure to bladder carcinogens. An independent evaluation of the data was then undertaken by the Epidemiology Resources, Inc. Working Group on Saccharin (Walker et al., 1982). They also concluded that there was no evidence for an association between bladder cancer and use of nonnutritive sweeteners. Their analysis of the sub-groups revealed that effects of the sweeteners were not consistent among the subgroups with similar baseline risk, and that dose response trends were not consistent and were subject to considerable sampling error (Walker et al., 1982).

Saccharin's long history of use in amounts normally consumed has not revealed any adverse health effects in humans. However, few data exist concerning saccharin's effects on two subgroups, young children and pregnant women, for which some concern has been indicated (NRC/NAS, 1978). The American Medical Association (AMA) supports the continuing availability of saccharin but suggests that consumption patterns and reports of adverse health effects associated with the use of saccharin should continue to be monitored and evaluated (AMA, 1985). All studies to date have been unable to establish a bonafide health risk to humans from the use of saccharin in normal dietary amounts.

Current Status. Although saccharin has been identified as a low-potency carcinogen and tumor promoter in male rats, suggestive of a potential risk to humans, epidemiological studies provide no evidence of increased risk of bladder cancer among users of artificial sweeteners, including saccharin. The AMA's Council on Scientific Affairs concluded that since there is no ideal sweetener for all foods, saccharin should continue to be available as a food additive (AMA, 1985).

Saccharin is currently approved for use in more than 80 countries and has been reviewed and determined to be safe by the Joint Expert Committee on Food Additives of the World Health Organization and the Scientific Committee for Food of the European Economic Communities. Also, many groups in the scientific and health communities have reviewed the experimental and epidemiological evidence and have issued statements in support of saccharin's usage. In the U.S. it is still provisionally listed in 21 CFR 180.37 on an interim basis pending additional studies and FDA action.

Cyclamate

This sweetener, discovered in 1937, is approximately 30 times sweeter than sucrose. It tastes very much like sugar and unlike aspartame and some other natural sweeteners it is heat stable. Cyclamate is available in the form of cyclamic acid, calcium cyclamate or sodium cyclamate. Cyclamate was first marketed as a dietetic aid in the U.S., by Abbott Laboratories, in the early 1950's and it became a popular sweetener in carbonated diet beverages in the 1960's in conjunction with saccharin because of its lack of aftertaste. This mixture also overcame the bitterness of saccharin.

Regulatory History. With the passage of the Food Additives ammendment in 1958, both cyclamate and saccharin were classified as GRAS. In 1969, evidence from a study of a saccharin/cyclamate mixture conducted by WARF implicated cyclamate as a possible cancer causing agent in rats (Price et al., 1970). Cyclamate was removed from the GRAS list on October 18, 1969 and FDA asked the manufacturer to submit a petition for its use as a food additive. Until such a petition could be approved, its use was terminated in foods and beverages and as an over-the-counter drug (34 FR 17063, October 21, 1969, 35 FR 13644, August 27, 1970, respectively). In Canada, its use was restricted to table top sweeteners but in 1978 cyclamate was approved again for use in pharmaceuticals. Cyclamate is permitted for use in low-calorie foods in 40 countries and Canada.

Subsequent research, however, failed to conclusively prove the carcinogenicity of cyclamate. The manufacturer of the sweetener petitioned FDA for approval of cyclamate as a new food additive several times, but after extensive debate, the petition was rejected in 1980. The 1980 decision of the FDA to reject the petition for cyclamate's approval was based not on the Delaney Clause but on the general safety clause of the Food, Drug and Cosmetic Act, stating that cyclamate had not been shown with a reasonable certainty to not cause cancer in man or animals or not be a mutagen (FDA, 1980). FDA is currently considering a second petition, filed for approval in 1982, based on additional scientific evidence (June, 1986).

Experimental Data. The study which prompted the cyclamate ban in the U.S. (Price et al., 1970) involved feeding rats high concentrations of a 10:1 mixture of cyclamate and saccharin. In addition, some of the rats received cyclohexylamine (CHA)—a compound which may be formed from cyclamate by bacteria in the lower gastrointestinal tract of some individuals. The experimental design prevented drawing an accurate conclusion based on the effects of cyclamate, saccharin, or CHA alone. Furthermore, some of the rats which developed bladder tumors also had bladder stones and/or bladder parasites which should have invalidated the study.

Saccharin's status was not considered at this time because it was only a minor component of the sweetener mixture and because it had not been shown to be hazardous in its long history of safe use. Another possible explanation for the results obtained in the study may have been the amount of sodium fed to the rats through the sodium and calcium salts of cyclamate; thus stressing the rats' urinary systems (ACSH, 1984). Subsequent animal studies investigating the effects of cyclamate, the 10:1 mixture and CHA conducted in mice, rats, dogs, hamsters and monkeys have not revealed a link between cyclamate and cancer.

Mutagenicity studies have been conducted and the majority have been negative (Cattanach, 1976). The review of these studies by Cattanach (1976) pointed out that those studies that are positive have not been reproducible or they have shown chromosomal breaks of uncertain significance. Cyclamate has not been shown to produce the chromosomal aberrations which actual mutagens produce in addition to breaks (Meisner and Inhorn, 1972).

In April 1984, after reviewing all data on cyclamate, FDA's Cancer Assessment Committee of the Center for Food Safety and Applied Nutrition concluded that "the collective weight of the many experiments intending to discriminate between the carcinogenicity and noncarcinogenicity of cyclamate indicates that cyclamate is not carcinogenic (ACSH, 1984). In 1985 the National Research Council pronounced the case closed, reporting that cyclamate is not carcinogenic and that no further research into that question is necessary (NRC, 1985). The National Academy of Sciences however, has raised questions concerning "promotion of carcinogenicity." The FDA is currently waiting for additional studies from the manufacturer before making a decision on cyclamates for use in foods. In addition, studies evaluating the overall human safety of cyclamate are in progress at FDA and other independent laboratories.

Cyclamate's reapproval would have numerous benefits for consumers, especially those on special diets, as these persons attempt to maintain desirable weight and good health. Cyclamate would broaden food applications for non-nutritive sweeteners, thus giving consumers a wider selection in their restrictive diets. The benefits appear to outweigh any undeterminable risk which may be associated with the use of cyclamates.

TRENDS IN SWEETENER CONSUMPTION

Per capita use of total caloric sweeteners has been relatively steady for the past decade. U.S. per capita disappearance of caloric sweeteners between the years 1975 and 1985 is listed in Table 3. These data, sometimes referred to as consumption data, are actually disappearance data: i.e., the total amount produced, minus exports, plus imports, divided by the population. Actual consumption will vary by individual and, in fact, some of the sugars are used in processes such as breadmaking to serve as yeast food; thus we do not consume the entire amount. The number also does not account for any waste or losses.

Americans are consuming less sucrose now than 10 years ago. We consumed an average 61.8 pounds of sucrose per person in 1985 compared with 89.2 pounds per person in 1975. While sucrose consumption has decreased, high fructose corn syrup (HFCS) consumption has increased from 5.0 pounds in 1975 to an estimated 42.7 pounds of HFCS per person in 1985. The estimated total per capita annual consumption of all nutritive sweeteners in 1985 was about 127.4 pounds, slightly higher than the 118.1 pounds consumed in 1975.

Consumption of reduced calorie sweeteners (aspartame and saccharin) has more than doubled since 1978 (CCC, 1985; USDA/ERS, 1985). Statistics from the U.S. Department of Agriculture showed that the average consumption of either aspartame or saccharin in 1984 was only about one-half an ounce per person (CCC, 1985). The sweetness equivalency of the low-calorie sweeteners relative to sugars (approximately 1/200), allows us to consume much smaller amounts of these sweeteners than the sugars.

These statistics reflect the changing needs and desires of American consumers. For a variety of reasons, we are more weight-conscious. A 1980 survey showed that more than 80 million Americans said they were making an effort to control their weight (CCC, 1985). Our desire to decrease sugar consumption and caloric intake is being met by the food industry through the application of a number of nutritive and non-nutritive sweeteners to a variety of foods and beverages.

CONCLUSION

The perfect sweetener does not exist. However, we do have a large variety of sweeteners available to us. Each one of these has specific applications as a result of certain advantages and limitations.

Not every sweetener is appropriate for the needs of every individual. Therefore, we need to continue to have a number of different sweeteners, nutritive and non-nutritive, available to us, to satisfy our flavor and texture requirements in foods and beverages and to satisfy our energy needs.

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Table 3—U.S. Per Capita Disappearance of Caloric Sweeteners, 1975-85[a]

Calendar year	Per capita consumption in pounds							
	Sugar (refined)	HFCS[b]	Other corn syrups	Glucose (dextrose)	Honey	Edible syrups	Total caloric sweeteners	Population
1975	89.2	5.0	17.5	5.0	1.0	0.4	118.1	216.0
1976	93.4	7.2	17.5	5.0	0.9	0.4	124.4	218.0
1977	94.2	9.5	17.6	4.1	1.0	0.4	126.8	220.2
1978	91.4	12.1	17.8	3.8	1.1	0.4	126.6	222.6
1979	89.3	14.9	17.9	3.6	1.0	0.4	127.1	225.1
1980	83.6	19.1	17.6	3.5	0.8	0.4	125.0	227.7
1981	79.4	23.2	17.8	3.5	0.8	0.4	125.1	230.0
1982	73.7	26.7	18.0	3.5	0.9	0.4	123.2	232.3
1983	71.1	30.7	18.0	3.5	0.9	0.4	124.6	234.5
1984	67.5	36.3	18.0	3.5	1.0	0.4	126.8	236.6
1985[c]	61.8	42.7	18.0	3.5	1.0	0.4	127.4	239.0

[a] USDA/ERS, 1985
[b] HFCS = High-fructose corn syrup
[c] Estimated

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Council Report

Aspartame

Review of Safety Issues

Council on Scientific Affairs

• This report examines the safety issues related to the nutritive sweetener aspartame, including possible toxic effects of aspartame's component amino acids, aspartic acid and phenylalanine, and its major decomposition products, methanol and diketopiperazine, and the potential synergistic effect of aspartame and dietary carbohydrate on brain neurochemicals. Available evidence suggests that consumption of aspartame by normal humans is safe and is not associated with serious adverse health effects. Individuals who need to control their phenylalanine intake should handle aspartame like any other source of phenylalanine.

(*JAMA* 1985;254:400-402)

ASPARTAME is a nutritive sweetener produced commercially from two amino acids, L-phenylalanine and L-aspartic acid. It is digested as a protein and provides 4 kcal/g.[1,2] Since aspartame is 180 to 200 times sweeter than sucrose, small amounts are needed to achieve equivalent sweetness.[3]

In 1974, the Food and Drug Administration (FDA) approved aspartame for use as a sweetener in foods such as cold breakfast cereals, chewing gum, dry beverage mixes, instant tea and coffee, gelatins, puddings, fillings, dairy product analogue toppings, and table-top sweeteners.[4] After formal objections were filed and because of a need to establish the authenticity of the research data on aspartame, the FDA stayed the regulation and appointed a public board of inquiry to investigate issues related to aspartame's safety. The manufacturer of aspartame, G. D. Searle & Co, agreed to delay the marketing of aspartame until safety issues could be resolved. On completing its review, the board of inquiry recommended withdrawing approval of aspartame until the question of its possible oncogenic effect could be resolved by additional studies.[5]

The FDA took issue with the board's recommendation and concluded that aspartame is safe for its proposed uses as a food additive. Thus, in 1981, the marketing stay was lifted and, in accordance with the 1974 ruling, aspartame was approved for use in foods.[6] In July 1983, aspartame was approved for use in carbonated beverages and carbonated beverage syrup bases.[7]

SAFETY ISSUES

The public board of inquiry was charged with addressing the following concerns: (1) the possibility that aspartame, either alone or in combination with glutamate, may contribute to brain damage, resulting in mental retardation or adversely affect the neuroendocrine regulatory system; and (2) the possibility that aspartame induces brain tumors in rats. In approving aspartame for use as a sweetener in foods and carbonated beverages, the FDA addressed these issues plus two others, namely, the stability of aspartame in liquid systems and the possibility that aspartame and dietary carbohydrate may have a synergistic effect on brain neurochemicals.

Brain Damage, Mental Retardation, and Endocrine Dysfunction

One objection to the 1974 approval was the possibility that aspartame, either alone or in combination with glutamate, might contribute to brain damage, mental retardation, or endocrine dysfunction. Both the public board of inquiry and the FDA examined the neurotoxic potential of aspartame's component amino acids, the plasma concentration at which each amino acid poses a risk of brain damage, and the amount of aspartame that must be consumed to elevate plasma phenylalanine and aspartate to hazardous levels.

Plasma phenylalanine concentration normally ranges from 6 to 12 µmole/dL. The toxic threshold for plasma phenylalanine is 100 µmole/dL for normal persons, including infants, and 50 µmole/dL for pregnant women (ie, due to the 1:2 ratio

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From the Council on Scientific Affairs, Division of Drugs and Technology, American Medical Association, Chicago.

This report was submitted to the Council on Scientific Affairs as an informational report at the annual meeting, June 1985.

This report is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all of the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and patterns of practice evolve. This report reflects the views of scientific experts and reports in the scientific literature as of June 1985.

Reprint requests to Council on Scientific Affairs, Division of Drugs and Technology, American Medical Association, 535 N Dearborn St, Chicago, IL 60610 (John C. Ballin, PhD).

gradient maintained by the placenta, a plasma phenylalanine level of 50 μmole/dL in a pregnant woman creates a level of 100 μmole/dL in her fetus). Clinical studies have shown that a loading dose of aspartame, 34 mg per kilogram of body weight (equivalent to the 99th percentile of projected aspartame consumption for an entire day) increased plasma phenylalanine concentration from a fasting level of 6 μmole/dL to 11 μmole/dL, a value within the normal range for adults and children. Only a loading dose of 200 mg per kilogram of aspartame increased plasma phenylalanine levels to 50 μmole/dL. This dose is equivalent to 600 aspartame tablets or 24 L of aspartame-sweetened beverage.[3] Thus, the FDA and the board of inquiry agreed that "the data establish that the proposed use of aspartame will not cause or aggravate the type of diffuse brain damage associated with sustained high plasma levels of phenylalanine."[8]

Individuals with phenylketonuria appear to metabolize aspartame adequately. In studies of adolescents[9] and adults[9,10] with phenylketonuria, the administration of aspartame in a single large dose (either 34 or 100 mg/kg) increased serum phenylalanine levels slightly. These levels were well below serum values associated with phenylalanine toxicity and returned to baseline values within a few hours. However, because individuals with phenylketonuria need to control their phenylalanine intake, products containing aspartame bear the statement "Phenylketonurics: contains phenylalanine."[10,3]

Regarding the aspartic acid moiety of aspartame, there was concern that aspartame, either alone or in combination with glutamate, may cause focal brain lesions and endocrine disorders. The combined plasma aspartate plus glutamate level was used to evaluate this issue because both aspartame and glutamate are capable of producing neurotoxic effects in rodents and are mutually additive in their effects; some ingested aspartame is transaminated to glutamate, and glutamate is widespread in the food supply, often as monosodium glutamate (MSG). Numerous studies have shown that MSG induces hypothalamic lesions and endocrine disorders in a variety of experimental animals.[3]

After evaluating MSG toxicity studies in infant mice, the most sensitive species, the board established a toxic plasma aspartame plus glutamate threshold level of 100 μmole/dL. Clinical studies have shown no significant increase in plasma concentration of aspartame plus glutamate in adults given a loading dose of aspartame, 34 mg per kilogram of body weight. A loading dose of aspartame, 200 mg/kg, increased plasma of aspartame plus glutamate from a baseline of 2.7 μmole/dL to 7 μmole/dL in adults.[3] In normal adults, the addition of aspartame to meals containing MSG did not increase plasma concentration of aspartame plus glutamate above values reported when only MSG was added to meals.[11] Infants appear to metabolize aspartame and its component amino acids as well as adults.[12,13]

After reviewing studies in infants, children, adolescents, normal adults, diabetics, lactating women, and obese and glutamate-sensitive individuals, both the board of inquiry and the FDA concluded that there is no evidence that aspartame, either alone or in combination with glutamate, contributes to brain damage, mental retardation, or endocrine dysfunction.[14]

Brain Tumors

In keeping with the requirements of the FDA's Center for Food Safety and Applied Nutrition for assessing the carcinogenic potential of food additives, G. D. Searle & Co submitted data from chronic feeding studies in mice and rats. Because all parties agreed that the mouse data were negative, the board was charged with evaluating whether aspartame or its decomposition product, diketopiperazine, induced brain neoplasms in the rat. Three rat studies were reviewed by the board: E-33/34, a 104-week study of aspartame, with exposure beginning after weaning; E-70, a two-generation study of aspartame, with exposure in utero, during lactation, and then for 104 weeks; and E-77/78, a 115-week study on diketopiperazine, with exposure beginning after weaning.[3] Both the board and the FDA agreed that the diketopiperazine study results were negative; they differed in their interpretation of the data from the aspartame studies.

In the E-33/34 study, there was a brain-tumor incidence of 3.75% in the aspartame-fed rats and 0.8% in the control rats. The incidence of brain tumors in the E-70 study was 2.5% in the aspartame-treated rats vs 3.5% in the control group. The board expressed concern that the E-33/34 data suggested a dose-response relationship with early tumor onset and described the 3.5% brain tumor incidence in the control group of the E-70 study as "bizarre." Based on these results, the board concluded that "aspartame, at least when administered in the huge quantities employed in these studies, may contribute to the development of brain tumors" and recommended withdrawing approval of aspartame until additional studies could be conducted.[3] The FDA took exception to this conclusion and found that the E-33/34 data did not suggest a dose-response relationship or early tumor onset and that the 3.5% incidence of brain tumors in the E-70 study fell within the expected bounds of spontaneous incidence for the study size and type of rat used. Hence, the FDA commissioner concluded that aspartame and its decomposition product, diketopiperazine, do not contribute to brain tumor formation in rats.[4]

Stability

One objection to the use of aspartame in liquid systems focused on the potential toxicity of its decomposition products, particularly diketopiperazine.[3] Aspartame is stable in dry foods but decomposes on prolonged exposure to high temperatures or in liquid systems; its stability in liquids depends on pH and temperature.[15] Studies on the sweetener's stability in carbonated beverages have shown that aspartame degrades to diketopiperazine and its component amino acids, aspartame, phenylalanine, plus aspartyl-L-phenylalanine, and methanol. In carbonated beverages stored for eight weeks at 20 °C (68 °F), 84% to 89% of the original aspartame added to the beverages remained; 3% to 4% of the added aspartame was degraded to diketopiperazine. Storage at 30 °C (86 °F) for eight weeks resulted in 62% of added aspartame remaining in the carbonated beverage, with 12% converted to diketopiperazine. The FDA concluded that "although this lack of stability might result in a marginally acceptable product, it would not lead to an unsafe product. Any concern over possible toxic effects from DKP [diketopiperazine] has been eliminated as a result of long-term animal studies conducted using DKP itself as the test compound." Proper storage, handling, and distribution of aspartame-containing beverages can control this problem.[7]

Approximately 10% by weight of aspartame is converted to methanol.[14] Concern about possible adverse health effects associated with the ingestion of methanol prompted the Arizona Dietetic Association, the Central Arizona District Dietetic Association, and Woodrow C. Monte, PhD, to file a petition calling for a tolerance regulation and an embargo in Arizona of carbonated beverages and carbonated beverage syrup bases containing aspartame. In issuing his decision on the petition, the director of the Arizona Department of Health Services reviewed data concerning methanol toxicity and concluded that the small amounts of methanol either preformed in beverages or released upon digestion of aspartame are of no concern.[14] The FDA reported that fruits and vegetables are also sources of dietary methanol and that, in clinical studies, measurable blood levels of methanol (subsequently metabolized to formate) have not been detected until loading doses of aspartame exceed the projected 99th percentile exposure level of 34 mg/kg.[7,15] Abuse doses of 200 mg/kg of aspartame have not been shown to increase blood formate concentrations over predosing levels.[16]

Aspartame, Dietary Carbohydrate and Neurotransmitters

Another concern expressed prior to the approval of aspartame for use in carbonated beverages was the possibility that aspartame might alter brain neurotransmitter activity, resulting in functional or behavioral changes. This comment provided details of a study of five fasted human subjects who received large doses of aspartame (1 g) in 2 qt of beverage followed by a confection containing 200 g of sucrose; plasma phenylalanine levels were increased with this treatment.[7] In rats, the administration of glucose (3 g/kg) and aspartame (200 mg/kg) by gavage increased brain levels of tyrosine and phenylalanine and decreased brain serotonin concentration. It has been argued that these changes in brain amino acid and biogenic amine levels in rats may have important behavioral implications for humans, particularly children.[17,18] However, a study[7] of infant monkeys receiving aspartame (up to 3,000 mg/kg) or phenylalanine (up to 1,650 mg/kg) in a liquid formula for nine months showed that, although plasma phenylalanine levels were extremely high, the animals grew and developed normally, showed no electroencephalographic abnormalities or seizures, and were not physically or behaviorally impaired when removed from the high aspartame-phenylalanine diets. After reviewing these and other data,[19] the FDA concluded that, although aspartame increased plasma and brain phenylalanine levels, there was no evidence that aspartame, either alone or in combination with dietary carbohydrates, altered neurotransmitter activity or behavior.[7]

COMMENT

Available evidence suggests that consumption of aspartame is safe except by individuals with homozygous phenylketonuria or other individuals needing to control their phenylalanine intake. In approving aspartame for use in carbonated beverages, the FDA commissioner concluded that the maximum projected consumption of aspartame from foods and beverages by normal children and adults was "far, far below any level even suspected of being toxic."[7] In addition, aspartame ingestion is not associated with serious adverse health effects. Recently, the Centers for Disease Control, at the request of the FDA, evaluated complaints the FDA had received from consumers related to consumption of products containing aspartame. Following interviews with 517 complainants, the Centers for Disease Control reported that the great variety of complaints were mild in nature and concluded that "although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide evidence for the existence of serious, widespread, adverse healh consequences attendant to the use of aspartame."[20]

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February 24, 1986

Honorable Strom Thurmond
Senate Office Building
Washington, D.C. 20510

Re: Aspartame

Dear Senator Thurmond:

In January of 1985, I suffered a Grand Mal seizure, was admitted to MUSC in Charleston where after extensive tests they could discover no reason for my seizure and in addition, they discovered that prior to the Grand Mal seizure, I had suffered from temporal lobe seizures since August of 1984 and wasn't even aware of what was wrong. I thought I was having problems of a hormone nature. Also during this period of time I had been suffering from severe, I mean extremely severe headaches which occurred just about every other day and eventually led to vomiting spells several times a month. I had been employed as a legal secretary at Hinds, Cowan & Strange here in Georgetown. I know you're acquainted with Doug Hinds and also worked for the firm when Claymon Grimes was still a member; had been there for over 13 years. I had begun to have problems dealing with the job, the people, my memory grew so bad it was starting to cause embarrassment to my employers who found it to be so out of nature for me they began to wonder if I was doing it on purpose. To make a long story short, I eventually ended up walking out on my job, after being in the work arena for 28 years, I did something that stupid.

While I was in the hospital (about 9 days) I realized that the headaches were gone, I felt great considering what I had just been through. I came home about 11:00 one morning, fixed me a diet soda and by that evening I felt a slight pain and by the next morning, the incapacitating headache was back. My husband and I sat down and tried to go through the elimination process to see what the difference was in the hospital. Our conclusion was the diet soda, so I threw out what I had and discontinued buying the soda with Nutrasweet. The headaches went away, my nerves began to settle and I felt fine.

On February 25th, while watching the Today show on t.v., I saw an interview with a man discussing Aspartame or Nutrasweet. He said they had documented stories of people who had suffered mood alterations, severe headaches and brain seizures from the use of Aspartame. I immediately took steps to get in touch with the gentleman, who was Rodney Leonard, who put me in touch with Dr. Richard Wurtman, with M.I.T. who is doing extensive research on this subject. He has all my medical records and a complete history of what I went through and feels quite sure I was a definite victim of Aspartame poisoning.

At that time I also wrote the FDA, Senator Hatch and Senator Metzenbaum. I heard from the FDA in May of 1985 when a Charleston representative came and talked to us, took notes and said he would file the initial complaint form and then I would receive a follow-up to fill out and that form would have my case number on it. To get a copy of my file I had only to request the same under the Freedom of Information Act. I have not heard anything from the FDA since that time and decided to go ahead and request my file anyway. They said the Center for Food Safety and Applied Nutrition had the file in Washington and would respond to my request (Assignment #V97722).

My main purpose in coming to you at this time is that not only are you my Senator but you are also in a position as Senate Judiciary Chairman to see that something is done about the total disregard for public safety that seems to have been established by irresponsible Corporate officers and Government officials allowing a product to be released on the open market that could do that much harm to me. It's too late to help me all that much but I've got to do everything in my power to keep it from happening to others. Maybe I'm only a small percentage but does that mean it's all right to destroy my life as long as it doesn't hurt too many more people? My career is gone, a job I loved and was good at, that I took pride in and worked hard at. My reptuation was tarnished in the legal community.

There's so much more that has happened, my ordeal with the seizure control medication and what it has done to me that I will be glad to cover in detail if you so desire. But for now, just let me say that unbeknown to my doctors, I decided to gradually withdraw from the medication so as not to cause a shock to my system and even though I was told a week without the medication could be extremely dangerous for me, I have gone over three months now with no medication; my mind is beginning to get back to normal, my nerves are settling somewhat and my husband says he feels at last he's getting his wife back. Best of all - NO SEIZURES!!

Please join in with Senator Metzenbaum in his efforts (Bill #S1557) before it's too late for others. I was lucky; my seizure was at night when my husband was next to me and he knew enough to get a spoon in my mouth or I could have died that night. I will be glad to answer any questions, testify at any hearing or talk to anyone, anytime, anyplace to get something done.

I have never written to you about anything but that I didn't receive a personal call from one of your assistants and that means a lot to me. Due to the importantance of this matter, however I do want to make a point of asking you to please acknowledge receipt of this letter so I can have that assurance that it was, in fact, brought to your personal attention. Again, if you would like copies of my orignal letter setting out everything in detail or if I can personally answer any of your questions, please call on me.

Thanking you for your consideration and assistance in this matter, I remain

Yours sincerely,

Doris E. Bookhart

DEB

TO: DR. RICHARD WURTMAN
MIT
E25-604
CAMBRIDGE, MA 02139

RE: ASPARTAME (Nutrasweet)

FROM: DORIS E. BOOKHART (White female, born 9/20/42)
P. O. Box 1128
Georgetown, S.C. 29442
(803) 546-3435

BACKGROUND: From June of 1983 to December of 1983, I was on an 800 calorie a day diet and lost about 60 pounds, then I leveled off and tried to maintain that weight. (185 to 125) I was a legal secretary for over 13 years, enjoyed my work, enjoyed the daily challenge, and was told I was one of the best; I took pride in my work, also.

AMOUNT OF DIET SODA CONSUMED: In September of 1983, the 2 liter bottles of Diet Coke became available in this area and I used them at home, consuming about 1 bottle per evening. In February or March of 1984, the 16 oz bottles of Diet Coke became available and we ordered them at work. At the peak of the warm weather period I imagine I drank 4-5 of those during the working hours (9:00 to 5:00) and then about a full botlle of the 2 liter of Diet Coke at home during the day. Also during the summer I fixed the Lite-Line Lemonade and would drink close to a gallon of that during the day in addition to one or two 16 oz bottles of Diet Coke, however I did not realize at the time the lemonade even had Nutrasweet in it.

MOOD CHANGES: I began to notice this around the latter part of 1983. I would come home from work and the least thing that happened would bring on a crying fit. I was so sensitive that someone could say "Good morning" to me and I would go off on a tangent. My husband felt it was the pressure of my job and told me several times he was going to make me quit. I began to believe it was the job, also, because I couldn't seem to cope with the simplest thing, co-workers and bosses alike seemed to get on my nerves and these were people I had known and loved all those years. In July of 1984, I walked off my job. (I had been in the work arena for 28 years and had never done such a thing.) The moodiness didn't quit, it just got worse. We felt it could be worrying about financial changes in our life. We just didn't know except that I wasn't the same woman my husband had known for 15 years, that's for sure.

HEADACHES: The headaches began sometime around November of 1983. I thought it was perhaps because we had a long summer and the pollen was high that year, although up to then I had never been bothered with bad sinuses, other than an occasional sinus headache which was easily taken care of by taking a no-drowziness Sinutab.

These headaches just didn't seem to respond to any treatment whatsoever. I started off with the Sinutab. By noon if it hadn't cleared up, I would take the generic form of tylenol. By late evening if it still hadn't cleared up, I would try to take an Alka-Seltzer Plus. I would take hot washclothes and put one on my head and one behind my neck to try and break it up, but that still didn't seem to help. By nighttime, I would have to go to bed as early as 9:00 or 9:30 because it hurt just to hold my head up.

In December, what I call my "sick headaches" started. In addition to the pain in my head, it seemed that by the middle of the day, the pain would be so severe, it would make me sick to my stomach. I tried eating crackers to absord any acid I might have on my stomach. When we would sit down to eat our evening meal, it was all I could do to get my food down. Then, usually about a hour or so later, I would be in the bathroom, vomiting violently. Sometimes, by the next day, I would be fine, but other times, I would wake up with the pain still in my head, but it seemed like most of the time, the generic tylenol would knock it out by then. The vomiting is what concerned my husband. We had been married 15 years and he had never seen me throw up, no matter how sick I got, not even with the flu or anything like that.

The severe headaches would come at least once, sometimes twice a week. The sick headaches with the vomiting would come at least once, maybe twice a month, but I never went a full week without a headache.

The last day, before the Grand Mal seizure occurred during the night, I had all three at once. I woke up with the severe headache, which did not respond to any treatment, thereby bringing on the sick headache by about noon that day and somewhere around 1:00 I started in with the "spells" and having all three at once really scared me to death. I called my doctor and told him I couldn't wait until February for my appointment, I had to see him right away. So they made my appointment for 4:30 the next day. I never made it.

TEMPORAL LOBE SEIZURES: These started the latter part of August of 1984, but, of course, I had no idea what they were. I kept blaming them on the possibility of an early "change of life" symptom brought on by hormone changes in my body.

The first one was while I was covering for a receptionist at a local law firm for two weeks. I was sitting there toward the end of the day and all of a sudden it was like I was two places at once. I remembered afterward that it began with a flash across my mind of a person from our past we hadn't seen in years. I played out an entire scene, lasting some 5-10 seconds or so. But I never lost consciousness, never blacked out, never lost touch of what was going on around me. The doctors called them hallucinations, however, I never thought of them as being that. I always thought you were hallucinating when you saw something that wasn't there and thought it was real. I always knew this was in my mind's eye but it was like I was there and here at the same time. It's very, very hard to describe or explain. The second one was when I got home that evening and when I was trying to tell my husband what had happened, another one came on. I forgot to say, when I came out of it, I felt a sick, nauseating feeling in the pit of my stomach and I was so scared, I was shaking and my palms were clammy. I'll never forget the feeling. Anyway, all the time I was experiencing the second one, I saw my husband jumping out of the pool, running toward me because I couldn't talk and he could see the strange look on my face. I found it difficult to talk during the seizures because of the queasy feeling that accompanied them. They always started with a familiar face or event flashing across my mind. Later that evening, I had two more, one was picturing the dog of a friend of ours we hadn't seen in ages, and again played out a short scene in my mind. Sometimes, they were feelings of deja vu, but not all the time.

They went away for a couple of months, showing up again in October, at which time I had 3-4 one day. I had another spell of them in November and by that time I had learned to recognize when one was coming on and tried to fight them off by shutting out the mental images. It may have lessened the severity of them, but the nausea and queasiness were still there. I still couldn't completely shut out the images. I remember at times, it wasn't a face from the past, but a familiar smell, (which by the way wasn't there) and the scenario would be something connected with the memory of that smell. By December, I became convinced that I was either going through the change or completely losing my mind. In January I made an appointment to see my doctor (gynecologist) in February.

GRAND MAL SEIZURE: On January 21, 1985, I had started having the "spells" about every half hour or so. I had become less and less incapacitated with them because I had learned to fight off the visions, or at least keep them to a minimum, however, there was still the sick queasy feeling going into and coming out of them. This day I started off with a severe headache, which turned into a sick headache, therefore making me have to deal with all three maladies at once.

By 9:00 that evening, they were coming every 15 minutes. At 10:30, I went to bed because of the severity of the pain, the nausea, and general exhaustion. By that time, they were coming every 9-12 minutes apart.

At 12:30, or thereabouts, I got up to go to the bathroom. At about 1:00 a.m., I have to rely on my husband's description because I certainly don't remember a thing:

He says I woke him up because the bed was shaking. He turned on the light to find my body arched, my eyes rolled back in my head, and my entire body violently jerking, not arms or legs, but my entire body. He knew my tongue had gone down, or was going down my throat, and knew enough to get to the kitchen and get a spoon. Even though my jaws had locked tight, he was able to get the spoon through a gap in my teeth and got my tongue out of my throat. He said when he got my tongue back out of my throat, I made a funny sound and went completely limp. He woke me up to make sure I was still alive and told me to lie still, he had called the ambulance. By the way, we figure the only reason I did not lose bodily fluids during the seizure is due to the fact I had gone to the bathroom not 20 minutes before that.

When the ambulance arrived, it was obvious I had suffered seizure activity, however, I felt fine and told them I thought my husband had had a bad dream. I didn't remember a thing. Then when he began telling them about my spells, I had no idea what he was talking about. It was hours later that everything began to fall into place.

HOSPITALIZATION: There were no available rooms in Georgetown or Charleston, so my family physician, W. W. Easterlin, Jr., advised them to give me a valium for the night, come back later to ER for a CAT scan, and then report to his office at 2:00 that afternoon. When Dr. Easterlin called to get the results of the CAT scan, he became quite concerned and immediately referred me to Dr. Phanor L. Perot at the Medical University Hospital in Charleston, who is head of Neurosurgery. Since no room was available, Dr. Perot's office said they would call immediately upon anything being open. I was admitted to MUSC on January 23, 1985.

TESTS: They immediately ran another CAT scan in Charleston. They did a full set of chest & head X-rays, I think. They did an EEG, then the next day, took me back down for another EEG because the operator didn't do something right and they didn't feel they got a clear reading. That same day they did an arteriogram. The next day or two later, they did another EEG, however, this time they didn't give me anything to eat for at least 12 hours and made me stay awake all night. They put the wires up my nose into my head for this one.

After all the tests proved negative for tumors, bleeding, or malformations (which they had originally diagnosed an arterio venuos malformation in the right temporal lobe,) I was referred to Dr. Jerome Kurent, who is a Neurologist at MUSC.

Dr. Kurent is now in charge of my outpatient care. He has placed me on 600 mgs per day of Tegretol. Every two months, I have to have a full blood test run for a complete white count, a tolerance level of Tegretol in the blood stream, and a liver function test.

AFTERMATH: I was in the hospital for nine days and I didn't have one headache all the time I was in there. The only thing I drank during that time was tea, coffee, 2% non-fat milk, and a lemon flavored ginger-ale. No diet soda at all. I had never gone for a week without a severe headache for over a year.

I came home on the 29th, about 11:00 a.m., and poured me a diet drink. By 10:00 a.m. the following morning, I had one of my sick headaches, I mean a lulu. My husband and I decided the only difference was the diet drink, so we tried doing without it for awile to see just for sure. I found some diet drink that did not have Nutrasweet in it and drank that. It is now April 11th, 1985, and I have yet to have a severe or sick headache. I had one or two sinus headaches and only then did I remember how a sinus headache actually felt and believe me, what I had been having were no sinus headaches. So the only thing we actually blamed on the Nutrasweet at that time was the headaches.

Then on February 25th, I saw an interview with Mr. Rodney Leonard with the Community Nutrition Institute on Today Show. I heard him describing to a "T" what I had been through, the mood changes, severe headaches, and brain seizures. I nearly fell out of my chair. The only proof I have of these being caused by the Nutrasweet (Aspartame) is the fact that the headaches have ceased, the moodiness has subsided, other than normal monthly cycles women go through maybe once or twice a month, and even those are less severe, and I have had no seizure activity whatsoever, even though I am on a low dosage of medicine from what I understand.

Naturally, I am angry now. I have been through a terrible physical shock, my husband has been put through mental anguish— he still has nightmares about that night —and I am afraid to be alone for fear I might have another attack and there would be no one to help me. I know I'll eventually get over that but it's a very frightening thing.

MEDICAL RECORDS: At your request, I have, this date, sent a written authorization to Dr. Kurent and the MUSC to release any and all medical records, i.e. admission, operative and discharge summaries, X-rays, CAT scans, EEG's, arteriogram and outpatient notes incident to my hospitalization.

Once you have all this information in your hands, if you need me to go through any sort of testing, I will be available at a minute's notice. I want to help in any way I can. It's too late for me, my whole life has been turned around. I will have to take medicine the rest of my life, I have to undergo expensive blood tests every two months, I have put on almost all the weight I originally lost. That started during the moodiness I went through. All during my diet, my attitude was terrific and I felt good about myself. Then I started gaining a little before all this happened, gained more while I was in the hospital, and when I started taking the Tegretol, if I didn't eat something 3 times a day when I took the pill, I politely went to sleep or walked around like a Zombie. Then the nerves of what I had been through and fear of reoccurrence made it worse, I always ate when I was nervous, not hungry. Maybe, just maybe, something I say or do can prevent this from happening to some other poor soul. Maybe my exprience will trigger recognition to someone else in time to prevent the damage being done. Had I known what I was going through, believe me I wouldn't have walked around for six months having temporal lobe seizures, or sat back and watched my whole personality changing. I love people and I love life and I always made people feel good just to be around me. Believe me, that sure changed, too. I'm getting back to my old self now and hopefully, I can get my physical appearance back to where I want it, too. Time will take care of all that.

If you do not hear from the hospital within the next week or so about my records, please let me know and I'll try to hurry them up.

Dr. Kurent's address is: Dr. Jerome Kurent, Department of Neurology, Medical University of South Carolina, 171 Ashley Avenue, Charleston, S.C., 29425. His phone number is (803) 792-3221. His secretary's name is Patricia Cook.

My best to you in your studies.

Sincerely,

(Mrs.) Doris E. Bookhart

cc: Dr. Sanford Miller
Bureau of Foods
Washington, S.C.

Senator Orrin Hatch (Rep)
Labor & Human Resources Comm.
Senate Office Building
Washington, S.C.

Senator Howard Metzenbaum (Dem)
Labor & Human Resources Comm.
Senate Office Building
Washington, D. C.

Mr. Rodney Leonard
Community Nutrition Institute
2001 S Street, N.W.
Washington, D.C. 20009

RECAP OF BLACKOUT ACTIVITY

RE: DORIS E. BOOKHART

4/29/85 Blackout episode occurred while typing. Sound of typewriter began to fade and the deposition I was typing was was the last conscious thought I had so the details of it was my first awakening thought. I woke up out of a deep, deep sleep with my head on the floor and my bottom still in the chair, with pain in my neck where I had jammed it in the fall. I remember a sickening feeling with light-headedness just before I went out. Was alone - no guess as to duration but feel it was short.

8 days

5/7/85 Blackout episode occurred in easy chair while watching TV. Felt that usual sickening nauseous feeling with a detached or totally disconnected feeling, e.g. it was like I was drawn up into the TV game show I was watching and everything that was happening on it was swimming around in my head. Again, because it was the last conscious thought I had, it was my first thought when I came out of it. It's an eerie feeling coming back - I have to fight the sleep off because it's so peaceful, I don't want to wake up. Lost good amount of body fluid this time. Again, I was alone so have no idea as to duration but still feel it was only a short period of time.

3 mos.

8/9/85 Blackout occurred at work (Hinds, Cowan & Strange). Co-worker said we were talking, my face went completely blank, my mouth dropped open and I just politely went bong onto the desk. I cut my head just above the eye which bled profusely but turned out not to be as deep as it looked. Did not lose body fluids this time. Was able to determine this time the duration was about 10-12 seconds.

10 days

8/19/85 Blackout at home during early morning. Husband said I made a strange noise & jerked my hand slightly. Only lasted a few seconds because he ran over and shook me. That seemed to cause a head pain (not headache) the rest of the day. Also had a depressed, generally sick feeling rest of the day.

17 days

9/5/85 Blackout at work. Had warning signal - told co-worker something was about to happen and she walked over keeping me from falling back on my head as I slipped out of the chair. She said my right hand was twisted into a gnarled shape and my arm was drawn up into my body, my eyes rolled back into my head. This time I lost a great amount of body fluid - had just gone to restroom 5 minutes before. Finished work and felt pretty good until late in afternoon when depression & exhaustion took over. Cried myself to sleep that night, was depressed the next day.

3 days

9/8/85 Blackout at home. Sickening, almost sweet nauseous feeling comes over me; I can recognize it more easily each time. Husband decided to just observe this time. Both hands twisted in gnarled shape, both arms drew up into my body; I jerked twice, then went completely limp and eyes rolled back into my head. Lasted 10-15 seconds or maybe longer. Rested, then fixed supper. Felt fine except for depression rest of the day & most of the next day. More fear and panic than depression.

-24 days

10-2-85 Passed out at typewriter - fell against wall, chair slid out from under me and apparently my head slid on down full force, hit phone jack, split head open requiring two stitches. Tired & listless for several days after.

10-17-85 Saw Dr. Pritchard - switched me to 400 mg per day of Dilantin

10-18-85 Definite upswing, spirits high, felt good; no dpression.

10-19-85 Weird, dopey feeling; slightly uncoordinated, drowsy, motor function slow in limbs - arms and legs don't seem to immediately respond to what brain tells them; unsteady walking; lights seem dim in room (like when you've been in snow on sunny day and them come inside); hearing is mutued (like when you have a head cold and your ears plug up causing echo in head); emotionally still on upswing.

10-20-85 Same reaction today. Husband says eyes very dilated like someone spaced out on drugs; feel good physically. Trying to keep in mind the doubling up on medication may take some adjustments so will not judge medication yet.

10-21-85 Tried staggering medication - Tegretol at 7:00, Dilantin at 12:00, Tegretol at 5:00, Dilantin at 7:00. Didn't work. Still like a Zombie. Will be only deaf, blind person that's totally seizure free if this keeps up.

10-22-85 Tried eating more to counteract medicine. Spirits low again, feel nerves getting jumpy. Feels like minor earthquake inside of me; I'm edgy, nervous, hands quivering slightly; still have problems with eyes and ears.

10-23-85 Had sensation of heart fluttering (like when you're watching scary movie and monster jumps out suddenly); your heart seems to go up in your throat and that eerie feeling runs down your spine. Seem to spill lot of things in left hand, it just turns over for no reason. Hot sensations in face.

10-24-85 Took only one dose of pills today, didn't seem to shoot me up quite so bad but still nervous and jumpy. Definite down feeling today, probably what an addict feels like when crashing, I don't know.

10-25-85 Reaction still same with only half doseage. Knees feel like jello, difficult to walk steady, have tendency to weave a lot. Had strange reaction I compare to when I used to take diet pills 20 years ago - tongue curled slight in mouth, touching front part of teeth & lips pressed tight, saliva flowing more freely. Feel really hyper, but emotionally down, lethargic, can't concentrate.

10-26-85 Reaction less severe when I only talk half dose but it takes five to six hours to level off, helps to eat, but eatting causes weight gain, adding to depression.

10-27-85 Really down today, cried a lot for no reason. Latter part of day chest turned red, looked like rash. By time I went to bed, my face was beat red and rash had covered chest, breasts, back. Had low grade fever of 99° to 100°.

10-28-85 Woke up this morning after very difficult night. Face is very very red, feel like I'm burning up, although fever is still low grade - slightly over 99° (NOTE: For almost a year my temperature has maintained a level of 97° or lower, rather than supposed normal of 98.6°) Rash is now over entire body, is probably also in my scalp since my head is itching, my eyes are burning and sore, look bloodshot. To be on safe side did not take any pills and called Dr. Pritchard. Even though I did not take pills last night, either, I still feel lethargic and droopy-eyed, still nervous although itching has aggravated that symptom.

Senator HATCH. I look forward to hearing from the rest of the witnesses as well, but let me just ask a couple of questions. I have a whole raft of questions, but I will only ask a few. Sen. Metzenbaum has said not too many, if I could avoid it.

Senator METZENBAUM. I want to be able to hear all the witnesses.

Senator HATCH. That is fine. I do, too.

Do you persist in your opinion that the 3,000 adverse reaction reports you have received are of no clinical importance?

Commissioner YOUNG. Yes, I do, and this is a relatively low incidence of adverse reactions compared to the large number of individuals who are using the product.

Senator HATCH. And you are used to more reactions than that in most-products?

Commissioner YOUNG. Yes, I am. We have an extensive adverse drug reaction reporting system where we have about 4,000 reports per year. We are seeing a very low number in aspartame. This does not mean that some individuals may not be allergic, and I try to point that out very clearly, and I will introduce those case reports for the record. But this is a low number. And also, unlike the drug reactions, where we see a single symptom coming forward, or a syndrome, we really see a number of vague symptoms, and I am particularly interested in looking at some of the research that we have with FAA that will focus on some of the cognitive and behavioral factors

Senator HATCH. Now, knowing that you have received substantive objections to uses of aspartame which you have approved, what is your intent in responding to those objections? How do your responses relate to approval of additional uses?

Commissioner YOUNG. At the moment, we are going to, on our own decision, look at answering the petitions that we have inhouse. We could technically approve other uses, but we have elected at this moment to focus on the questions sc that we can take the extra precaution of being sure that we answer everything, and this will be done on a scientific basis, question by question.

Senator HATCH. Okay. Has the Center noticed an increase in adverse reaction reports associated with the publicity on aspartame?

Commissioner YOUNG. Yes, we have. We usually see a peak of adverse reactions with publicity. That is to be expected, and that is true in a variety of other adverse reactions that we have seen as well—for example, sulfites; we have seen this in regard to some of the drugs that we have had adverse reactions on, also.

Senator HATCH. Okay. Now, Dr. Young, we have three witnesses with us this morning who will testify that they have experienced adverse reactions to aspartame. These are: Mr. Larry Taylor, Mrs. Sharon Flynn Royal, and Major Michael Collings. A fourth witness on the particular panel, Dr. Alfred Miller, will testify about reactions some of his patients have had to aspartame.

Have any of these witnesses filed complaints with the FDA, and if so, would you share with us what FDA has done in response to these particular complaints?

Commissioner YOUNG. Surely. Let me answer that person-by-person. And I would like to first state that FDA realizes that there will be some allergic reactions, and there may be some idiosyncratic reactions. And what I am about to say should not detract in any way from the concerned patient who has proven on challenge to have an allergic reaction.

In the cases that you cited, for Dr. Alfred Miller, there is no record of a complaint from San Antonio in our adverse reaction monitoring system. We do not have any record of a complaint from Mr. Taylor of Arlington, Texas in the adverse reaction system. It was my impression that Mr. Taylor was one of the number of people from the Aspartame Consumer Safety Network who conferred with the Center on August 28 and 31 in 1987. We are not sure that that is the correct Mr. Taylor. If it is, he stated that he would soon be sending a record of his experience to us. That particular Mr. Taylor, if it is the same one, has not submitted any record to date, and we would be most interested in having this record.

We also have no record from Michael Collings, of either Nevada or Alabama.

In the case of Ms. Sharon Flynn, we do have a Project Number 4681 and the Complaint Number ORL2257———

Senator METZENBAUM. She will not be testifying today.

Senator HATCH. She will not be, okay.

Commissioner YOUNG [contining]. And that record is in the Parklawn Building. I do not feel it is appropriate to go over the record in public, but we do have that record available.

Senator HATCH. Will you please review with us the allegation that consumer complaints are not being properly addressed by FDA?

Commissioner YOUNG. We have addressed each of the complaints as they have come in. We have established the adverse reaction system. I have asked this to be strengthened under the Action Plan, which was previously submitted for the record. We have also reviewed this with Dr. Gerald Faich, who is the Director of Epidemiology in the Drug Adverse Reaction Monitoring System.

We have no substantial backlog of these complaints. There have been 3,500 processed out of about the 3,800 that we received. When we do get a complaint, we evaluate it within the Center. After evaluating it, we send an inspector out to obtain the records if we can. Once we obtain the records, we look at them medically.

As a pathologist, I must say it is very hard to establish cause and effect unless there is a single syndrome that is associated with it, and the symptoms that I put up there in my testimony and the background that I provided showed a wide variety of vague symptoms, and it is very hard to attribute these. Wherever we have had the medical record, we have not been able to get a cause and effect, with the exception of the cases of urticaria and panniculitis, which were very well-documented—just what should be done—a challenge study; and one could show that on the aspartame, one did get an allergic reaction; when taken off the aspartame, one did not. I believe that is 3 out of the 3,500.

Senator HATCH. Thank you. I am going to submit most of my questions, but I am just going to ask two more quickly. So with your permission, I will submit most of my questions for the record and request that you answer them.

Senator METZENBAUM. Without objection.

Senator HATCH. Since Dr. Wurtman has been particularly active in his scientific interest concerning the use of aspartame, and since your agency's interests are involved with ascertaining the safety of aspartame, why has not the FDA sponsored Dr. Wurtman's proposal to study the neurochemical effects of aspartame?

Commissioner YOUNG. We had a first cycle of grant applications, and when that cycle of applications was considered, Dr. Wurtman was one of the individuals who had put in a grant proposal. Regretfully, that first round had to be aborted because of some of the funding constraints within the agency. Also, the magnitude of Dr. Wurtman's grant, laudatory as it was, would have consumed more resources than we ever could allocate out of the $3 million that we have per annum to handle all the extramural research in foods.

We did put out a second round of applications that resulted in the application that I mentioned that we did award, and Dr. Wurtman did not apply for the second round to the best of my knowledge.

We would be delighted to have any eminent scientists compete, but we cannot target a grant or contract for an individual. That would be a violation of the law. It has to be competed for in a fair and open competition as judged by the agency.

Senator HATCH. I see. Could you estimate the amount of resources invested by FDA to study the safety of aspartame?

Commissioner YOUNG. It would be in the millions and millions of dollars. Our grants alone are in excess of $800,000. If one looks at the average manpower that we have put in, it would be in the millions. I would be happy to provide the best estimate that I can for the record.

[Information supplied follows:]

Estimate of Agency Resources Utilized for Aspartame Regulation

Center for Food Safety and Applied Nutrition

	1971-73	1974-77	1978-80	1981-83	1984-Present
Division of Toxicology	6.0[1]	12.0	7.5	4.5	4.0
Division of Chemistry and Food Technology	0.25	0	0.1	0.35	1.0
Division of Food and Color Additives	1.0	2.0	2.0	1.0	3.0
Division of Compliance	0.1	0.1	0.1	0.1	0.1
Division of Nutrition	0.25	0.25	0.1	0.1	5.0
Office of General Counsel	0.25	0.25	0.25	0.25	0.5
Office of Regulatory Affairs	0	0	0	0	7.2
	7.85	14.6	10.05	6.3	20.8 = 59.6

[1] Number represents the Full Time Equivalents devoted to aspartame regulation for this time period.

Converting FTE Estimates To Dollar Estimates for Resources Used in Aspartame Regulation

The usual practice followed in the Center Program Branch in converting FTE's to dollars is to take the direct FTE's engaging in the activity of interest; multiply them by two to account for clerical, managerial, administrative, and laboratory support; and finally multiply by the dollar amount given to us by the Division of Financial Management as representing the budget cost of an FTE. This latter cost is currently $60,000. Obviously, this cost has changed over time. Multiplying an FTE figure from the past by the current cost does not inflation adjust the past cost since FDA budgets have not kept pace with inflation. It does, however, provide a value of what those part FTE's would currently cost. Therefore, the FTE estimate of 59.6 yields a dollar estimate of 59.6 X 2 X $60,000 = [$7,152,000]

Senator HATCH. Would you do that? Would it be disproportionate with regard to other similar——

Commissioner YOUNG. It clearly is greatly disproportionate to any of the other things that are going on in the Center, and I must say that of the food issues that I have been concerned with, this has occupied more of my own personal time and more of the Center's time than anything that I have seen.

Senator HATCH. So you have had to comply both with scientific and political and legal requests in this matter as well?

Commissioner YOUNG. Yes, we have.

Senator HATCH. Now, I would submit for the record, Mr. Chairman, Senator Thurmond's statement; and then, also for the record, statements of Dr. Shaywitz, Dr. Booker, Dr. Levy, Dr. Porter and Dr. Kaufman.

Senator METZENBAUM. We will put those in the record, but not at the same point.

Senator HATCH. That is right. We will put them in the appropriate place.

[The prepared statements of Drs. Shaywitz, Booker, and Levy follow:]

Written Statement of

Bennett A. Shaywitz, M.D.
Director, Pediatric Neurology
Yale University School of Medicine

To the Labor and Human Resources Committee
United States Senate

I would like to submit the following statement for the Committee's consideration regarding the Senate hearings on aspartame.

I am Director of Pediatric Neurology and Associate Professor of Pediatrics, Neurology, and Child Study Center at Yale University School of Medicine. I have devoted the better part of my life to study and research in the field of neurology and to treat children with neurological disorders.

My colleagues and I at Yale are now conducting several clinical studies with aspartame. Several years ago, I first read in the newspaper of a possible link between the consumption of aspartame and seizures in people. As a student of the field of epilepsy, I found this curious since no scientific studies had been conducted showing such a link. However, newspapers seemed to report this as a scientific fact. Nevertheless, I began to look into this issue carefully, because if such a link were true, it would be extremely important for me to know this in order for me to effectively treat my patients.

In my personal evaluation and research since that time, I have found no clinical evidence in humans, nor any other reason to believe, that there is a relationship between aspartame consumption and seizures.

Questions about such a link have been raised based on anecdotal reports and some research in rats and mice that were given chemicals to cause seizures. First, let's examine the anecdotal reports.

As background, when an individual believes he has suffered a malady after consuming a product, that is considered an anecdotal report. It is usually not corroborated by a physician, nor does it determine cause and effect scientifically. This is what we are dealing with in discussing anecdotal complaints about seizures or, for that matter, any other complaint.

Anecdotal reports of seizures in humans have been investigated by the Food and Drug Administration and the Centers for Disease Control. In a 1984 report, the CDC concluded that it "could not find convincing evidence that any of the documented seizures had a high probability of being due to aspartame-containing products."

In its review of approximately 100 seizure reports since the CDC analysis, the FDA concluded in November 1986 that there is "no consistent association between occurrence of seizures in people and consumption of aspartame-containing products." This conclusion was announced by the FDA as it formally rejected a petition claiming that reports of seizures showed an imminent public health hazard.

In rejecting the petition, the FDA noted that approximately one percent of the American population suffers from seizures and that epilepsy is second only to stroke as the leading neurological disorder in the United States. The FDA further commented that:

> Under these circumstances and, because aspartame is frequently consumed by large numbers of people, it is not surprising that there may be a chance occurrence of seizure activity following ingestion of aspartame by seizure-prone people. Such a happenstance, however, is not indicative of a causal relationship between consumption of aspartame and the onset of seizure activity. In fact, such a happenstance would not be unexpected.

It is well known that most seizures are idiopathic, i.e. of undetermined etiology. However, we know that seizure susceptibility can also be related to many factors, including excessive consumption of alcoholic beverages, severe dieting, excessive fluid intake and hormonal variations.

Other allegations of a link between aspartame consumption and seizures have been based on reports in rats and mice which have first been treated with a seizure-producing drug. These experiments in no way parallel actual exposure by humans. Recent studies reported by a group at the University of Illinois clearly showed that high doses of aspartame had no effect in genetically-seizure prone rats, a more appropriate animal model. Other tests have found no effect of very large doses of phenylalanine, a component of aspartame, on seizures in the baboon, a species which more closely approximates man.

Because experimental models of epilepsy are limited in many respects and may resemble only certain aspects of the human disorder, the best scientific way to evaluate either anecdotal reports or the relevance of rodent models to the way humans actually consume aspartame in the diet is through controlled clinical studies in people. That is why we are currently conducting clinical studies. While there is no evidence that would make me, as a neurologist, believe aspartame might cause a seizure, it is simply prudent to carefully investigate individuals who claim they have had such a reaction or who might theoretically be at risk.

We are examining the effects of aspartame in several different groups -- children whose families believe they have had a seizure related to aspartame, children who have epilepsy, and children with a condition called attention deficit disorder. While our work has not yet been completed, we have found no data thus far that would indicate that aspartame is linked to seizures or behavioral changes. Regarding the issue of neurobehavioral changes, these findings are consistent with the overwhelming scientific evidence regarding the lack of an association between aspartame and behavioral changes. Double-blind, placebo-controlled studies are also ongoing at the Mt. Sinai Hospital in New York investigating adults who believe that they have had a seizure associated with aspartame.

Recently, research done at Emory University implied an effect of aspartame on human brain function. Distinguished colleagues and I have personally reviewed the methodology and study design which was used in these investigations. I can assure you that these conclusions are not supported by the data and unfortunately serve only to mislead the scientific community as well as the public.

Finally, let me mention the ongoing scientific review of this question by leading medical professional groups, including those examining aspartame's safety for special populations. The American Medical Association's Council of Scientific Affairs issued a report concluding that aspartame is safe for the general population. Among the medical community directly focusing on people with seizures, neither the Epilepsy Foundation of America nor the Epilepsy Institute recommend that people with epilepsy restrict their use of aspartame.

The Epilepsy Foundation of America has reported and I quote, "After study and review of available scientific reports, the Client Services Committee of the Epilepsy Foundation of America's Professional Advisory Board has concluded that at present, there is insufficient evidence to suggest that aspartame, a sugar substitute, should not be used by people with epilepsy."

After reviewing the scientific evidence and the seizure activity of some 5,000 patients over a three-year period, the Professional Advisory Board of the Epilepsy Institute of New York concluded, "As an organization devoted to people suffering from seizure-related problems, [we]...investigated these allegations and found aspartame to be safe for people with epilepsy."

In conclusion, I would strongly urge the committee to consider the distinction between solid scientific evidence presented in peer-reviewed journals, compared with theoretical questions and preliminary data. I would also indicate that studies in animals with extremely high doses of aspartame do not have any relevance to humans. Well-conducted studies, such as those human clinical trials I have just mentioned, that will be peer-reviewed and published in the scientific literature, provide the only credible means to draw accurate scientific conclusions.

Thank you for your consideration.

Bennett A. Shaywitz, M.D.
Director, Pediatric Neurology
Yale University School of Medicine

31 October 1987

Nancy Taylor
Committee on Labor and Human Resources
U.S. Senate
Rm. 835 Hart Building
Washington D.C. 20510

Dear Nancy Taylor:

Although the information given below is a matter of record I am speaking as an individual rather than representing the Epilepsy Foundation of America.

From April 1985 to April 1987 I was Chairman of the Professional Advisory Board of the Epilepsy Foundation of America. During that time I appointed an Ad Hoc Committee to review and to monitor continuously the bio-medical literature on aspartame and to advise the board if they found any reasonable evidence to suggest that aspartame might present a hazzard to people with epilepsy. The committee consisted of a distinguished neurologist-neurochemist and an equally distinguished pharmacologist, Dr. Carter Snead and Dr Dixon Woodbury. I was, of course, privy to their reports. As of the last meeting of the Board (April, 1987), their report was that, in their opinion, there was no valid, scientific evidence that aspartame posed any risk for people with epilepsy.

Respectfully,

Harold E Booker M.D.

Harold E. Booker, M.D.
9205 Terwilliger's Wood Court
Cincinnati OH 45249

The Children's Hospital • Boston

300 Longwood Avenue, Boston, Massachusetts 02115, Telephone (617) 735-7945
Northeastern Contributing Center
National Maternal PKU Collaborative Study

Harvey L. Levy, M.D.
Principal Investigator

Susan E. Waisbren, Ph.D.
Co-Investigator

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To the Committee on Labor and Human Resources, U.S. Senate:

I am a pediatrician and biochemical geneticist who for two decades has specialized in the diagnosis, treatment and research of those metabolic disorders known as inborn errors of metabolism. Among the disorders with which I have had extensive experience is phenylketonuria, often referred to as PKU. This is an inborn error which is associated with a greatly increased concentration of the amino acid phenylalanine. I wish to state my opinion about whether the aspartame in our diet will raise the level of phenylalanine in normal persons sufficient to be toxic to the brain of the ingesting individual or to the fetus of a pregnant woman. I am aware of concern about this, prompted by our knowledge that PKU when untreated results in mental retardation and that untreated PKU in the pregnant woman (maternal PKU) causes damage to the fetus.

In my view this concern is unfounded at the present level of aspartame ingestion. It might also be unfounded at an even higher level of aspartame use in our society.

First, let me address the fear that aspartame use will cause sufficient hyperphenylalaninemia to damage the ingesting individual. The universal experience is that for recognizable brain damage to occur from hyperphenylalaninemia, the level of phenylalanine in the blood must be consistently higher than 600 uM (10 mg/dl). People with PKU, for instance, have blood phenylalanine levels at least 1000 uM (16 mg/dl) and usually 1200 uM (20 mg/dl) or higher. It is likely that this elevation must be present throughout infancy and early childhood if damage is to occur, since that is the period when the brain is most vulnerable to biochemical abnormalities. In a collaborative study Dr. Richard Wurtman of MIT and we found that normal individuals or even those who are carriers of the gene for PKU responded to a large amount of aspartame ingested at one sitting with blood phenylalanine levels that were usually well below 100 uM (1.7 mg/dl) and never above 120 uM (2 mg/dl). In fact, all of the levels remained within normal limits. None even remotely approached the value of 600 uM or higher that might be considered toxic to the brain. Furthermore, the brain damage observed from PKU is associated with a consistent increase in the blood phenylalanine level. Aspartame ingestion provides phenylalanine only intermittently. Thus, the phenylalanine response to quite substantial amounts of aspartame ingested by those who do not have PKU does not appear to be such that would endanger the brain.

Now, I address the fear that aspartame ingested by pregnant women will produce increases in their blood phenylalanine levels that will cause fetal damage evident as birth defects in their children. In our most recent published study of the effects of maternal PKU and other degrees of maternal hyperphenylalaninemia, Dr. Susan Waisbren and I found that women with blood phenylalanine levels as high as 600 uM had normal children. In fact, the average IQ of their children was higher than what is considered to be the average for normal children in our society. Thus, if our experiences with blood phenylalanine responses to aspartame ingestion cited above apply to pregnant women (and there is no reason to believe they do not), it would appear that the amount of aspartame presumably ingested by normal pregnant women, including those who carry the PKU gene, does not produce a blood phenylalanine level even close to that which would endanger the fetus.

I hope that this information and these opinions will be helpful to you in your deliberations. Thank you.

Sincerely,

Harvey L. Levy, M.D.
Director, Biochemical Genetics

Associate Professor of Neurology
Harvard Medical School

Senator HATCH. Thank you, Dr. Young. Commissioner, I think you do a terrific job. Like I say, I could not be any more supportive of an agency than I am of the FDA, and I hope that we in this Committee and those of us in the appropriations process will start taking into consideration how important it is to provide the best facilities in the world for you people to do your work and research. You are doing it in an efficient, highly scientific way now, yet under less than local circumstances.

Commissioner YOUNG. I certainly appreciate that.

Senator HATCH. I think what we must upgrade your facilities and help in every way possible. In spite of the poor facilities, you still do the highest quality work anywhere in the world today in the field that you oversee. I want to personally express my gratitude on behalf of the American people to you and the other folks at FDA for the great work you do.

Commissioner YOUNG. Thank you, Senator. I have been particularly proud to serve. I think the agency does a magnificent job amid all the pressure it has, and particularly with the poor facilities, it is very hard to recruit people. And I am just delighted to hear you focus on that and focus on the resources that are required to do the job. It actually costs the American people less than $2 per man, woman and child per year for all the services that FDA provides. We do an annual update on how Government agencies are viewed, and I have been told by our staff that we rank second amongst the administrative agencies. The highest one is the Park Service. To my knowledge, no one has ever camped out in the Parklawn Building for recreation, and in that sense it is a very high regard by the American people, and I am just honored to serve there.

Senator HATCH. Well, thank you, sir.

Senator METZENBAUM. Thank you very much, Dr. Young, and all the members of your staff. We are always pleased to work with you and look forward to working with you on other matters as well.

Commissioner YOUNG. Thank you, and we will be delighted to provide anything we can for the record. And thank you for giving me the opportunity of presenting those charts.

Senator METZENBAUM. Thank you.

Our next witnesses will be Mr. Larry Taylor, Maj. Michael Collings, Dr. Alfred Miller, and Mr. Jim Turner.

Gentlemen, and all the following witnesses, I will tell you now that we will adhere to a strict five-minute rule so that any testimony in excess of that, we are going to have to cut you off.

Mr. Taylor, we are happy to have you with us today, sir. Will you please identify yourself?

STATEMENTS OF LARRY TAYLOR, CERTIFIED REGISTERED NURSE ANESTHETIST, ARLINGTON, TX; MAJ. MICHAEL COLLINGS, TYNDALL AIR FORCE BASE, LYNN HAVEN, FL; DR. ALFRED MILLER, PHYSICIAN, SAN ANTONIO, TX, AND JIM TURNER, ATTORNEY, COMMUNITY NUTRITION INSTITUTE, WASHINGTON, DC

Mr. TAYLOR. Thank you, Senator.

I am Larry Taylor, a Certified Registered Nurse Anesthetist from Arlington, Texas.

At the age of 35, I experienced three grand mal seizures. The seizures were diagnosed as idiopathic. Because of my profession as a certified registered nurse anesthetist, I was not allowed to totally return to my anesthesia practice for two months after the first seizure.

On December 23, 1985, I experienced a second, less severe grand mal seizure. This occurred in the surgical suite just prior to administering a spinal anesthetic. On January 28, 1987, I experienced my last seizure.

The events leading up to my seizures are well-documented. In the fall of 1983, I began having visual disturbances making it difficult to see the monitors in surgery and to fill out my anesthesia record. Following the onset of visual disturbances, I began having severe headaches. Not long after, I began to feel as if I could not remember as well. The headaches and visual disturbances became more frequent until I was urged to see a neurologist.

I saw a neurologist, and his diagnosis, after a CAT scan, EEG, and an infantile memory test, was "common migraine". I was placed on Ergomar as necessary to alleviate the headaches. I took this medication from September 1984 to October 1985, when I had my first seizure. During the interim, I began having laughing seizures. I developed the hives in August 1984 and was placed on Benadryl.

My ingestion of NutraSweet at this time was approximately four to six Diet Cokes daily, and very infrequently, two packages of Equal on dry cereal.

Between my first and second seizures, I asked my neurologist about aspartame and a possible link to seizures. She said she did not know, but that she would research the possibility. After my third seizures, she said, "Wouldn't it be a shame if that is all that is wrong with you is NutraSweet?" She had me take the NutraSweet out of my diet, and my health has improved ever since.

My problems are now reobtaining my malpractice insurance and getting my privileges back. I have only one small hospital where I could practice and one plastic surgeon's office. As of yet, I have not been reinstated with malpractice insurance.

It is now two years since my first seizure. I am still on medication. I am still not working in anesthesia, and I am still collecting my disability insurance.

Senator METZENBAUM. I have just a few questions for you, Mr. Taylor.

Have you ever had any neurological disorders or any other problems which could explain your seizures?

Mr. TAYLOR. No, sir.

Senator METZENBAUM. You underwent extensive neurological testing. You had a CAT scan, and an EEG?

Mr. TAYLOR. Yes, sir.

Senator METZENBAUM. Did you have an MRI?

Mr. TAYLOR. Yes, sir. I had two of those.

Senator METZENBAUM. Anything else?

Mr. TAYLOR. I had an arterial angiography also done; numerous blood work studies and things, and an EKO-cardiogram.

Senator **Metzenbaum**. And they found nothing?

Mr. **Taylor**. Absolutely nothing.

Senator **Metzenbaum**. And you were consuming four to six diet drinks daily, and then you stopped. When did you stop those in relation to the third seizure?

Mr. **Taylor**. I think a day or two afterwards.

Senator **Metzenbaum**. Why did you stop?

Mr. **Taylor**. Well, my neurologist and I had been talking about, between the second and third seizures, about the possibility of NutraSweet being my problem, and so we figured, well, if we could not find anything else that was wrong with me, why not try that.

Senator **Metzenbaum**. Let me quote from a letter from your doctor, who is a neurologist.

> When I saw him last, I had basically suggested that since there was some question as to whether or not NutraSweet might play any role, it is best to discontinue it. He has not had any further seizures, and is really not having any problem from his medication at this point in time.

Is that pretty accurate?

Mr. **Taylor**. That is accurate, yes, sir.

Senator **Metzenbaum**. According to your doctor, you were initially on the anti-seizure drug Dilantin, but you had more seizures even while you were on the drug, didn't you?

Mr. **Taylor**. Yes, sir, I certainly did.

Senator **Metzenbaum**. I have a number of letters that your doctor has written on your behalf to hospitals and others, trying to get you reinstated with your work. One says, "There remains a question as to whether or not all of this is a result of consuming NutraSweet. Unfortunately, there is neither a 'yes' or 'no' available on that issue."

That is also my concern, Mr. Taylor, and I am hopeful that these hearings will put us on the road to finding an answer for you and thousands of other consumers who have similar concerns.

I appreciate your testimony.

Mr. **Taylor**. I appreciate your concern, sir.

Senator **Metzenbaum**. Thank you.

Major Michael Collings, of Tyndall Air Force Base.

Major **Collings**. Hello, sir.

I am Major Mike Collings, and I am currently stationed at Tyndall Air Force Base in Florida.

To make a long story short, back in about August of 1983 I began having tremors in my left arm. The tremors were uncontrollable, and they were always preceded by a type of an aura. This aura would best be explained by butterflies in your stomach, similar to going over a hill in your car or on a roller coaster, that type of feeling.

They were very irregular, and came in groups, if you will, one or two or three at a time, in a period of maybe 24 hours, and then they were spaced out over the next week or two weeks, I could possibly have none.

During this period of time, I was consuming large amounts of Kool Aid sweetened with NutraSweet. When I say "large amounts", there were days that I would probably drink around a gallon a day. I would say that my average consumption was in the neighborhood of three quarts.

I am a big runner and was running at that time between five and eight miles, three to four times a week, and I used that to keep my hydration level up. Also, I was flying F16 fighter aircraft and had a tendency, in the Nevada heat, to get very dehydrated, and carried that Kool Aid with me to work, as well as drinking Diet Cokes.

The tremor continued through about December of 1983, at which time, in early January, I was stationed at Kunsan Air Base, which is a remote tour in the Republic of Korea. I am not exactly sure, but I can definitely say by February of that year 1984, my tremors had gone.

My mind is now in relief that they are no longer there. I do not know why they quit. But around June of 1984, they began again. I can relate this to June because I had a sprained ankle, and to a runner, that is a very significant event in his past, where I could not run. I remember having a tremor while I was on the crutches. And just prior to having my sprained ankle, I had made a trip to another air base not so remote as Kunsan and purchased some Crystal Lite, which was sweetened with NutraSweet and again, my consumption rate was probably around a gallon a day.

I had a big concern about sugar ingestion and did not want to do that and keep the calories low.

Sometime later, in the July time frame—well, shortly thereafter, my seizures or tremors had quit—but in November I had returned from a deployment from Australia and had received a care package, if you will, from home, and in that care package was some Kool Aid sweetened with NutraSweet. I began consumption again, I would say in the gallon to three-quart arena, and my tremor came back.

At this particular time, I did have one that was significantly worse, where the tremor was up in my arm, into my neck, and caused me to spin around a couple times.

After that particular instance, I had no more until I returned to the States back from my year remote tour, and that was the end of January. I am not sure exactly when, whether it was the end of January or the first part of February, but I can definitely say by the end of February of 1985, my tremors began to come back. Throughout the rest of that year, until the culmination of October 1985, when I had a grand mal seizure, the tremors increased in severity and also in frequency.

On 4 October, I had a grand mal seizure while I was walking out to be the supervisor of flying at the base of the control tower.

Senator METZENBAUM. To be what?

Major COLLINGS. Supervisor of flying is the duty I was about to have; and I had a seizure in the parking lot which was witnessed by a young airman.

Prior to that, my consumption of NutraSweet had remained pretty constant in the last six months, in the neighborhood of three quarts to a gallon.

That morning, four hours prior to having my seizure, I had just stepped out of an air-to-air flight in an F-16 and was very fortunate, I felt, that the seizure did not occur while I was flying the airplane.

Since then, I spent three days in the hospital at the time I had that seizure. My father talked to me the last day I was in the hospital, and had mentioned something to me about an association with NutraSweet and neurological disorders, which I believe was around the 6th of October. I quit drinking NutraSweet that day, and did not have any seizures or tremors from this point on. Around the 21st of October, they sent me down to Wilford Hall, which is the big medical center in San Antonio, and they put me on a drug called Dilantin. Since the day I quit NutraSweet and in conjunction with that Dilantin, which is over two years now, I have not had a tremor in my left arm and/or any type of neurological disorders.

[The prepared statement of Major Collings follows:]

STATEMENT BY MAJOR MICHAEL COLLINGS

COMMITTEE ON LABOR AND HUMAN RESOURCES

"NUTRASWEET: HEALTH AND SAFETY CONCERNS"

NOVEMBER 3, 1987

28 October 1987

The following is a brief historical account of my medical problems from August 1983 through October 1985:

In August 1983, I began having a light tremor in my left arm. The tremor was uncontrollable, lasted a few seconds, and was always preceded by an "aura" similar to what is known as "butterflies" in the stomach. I know for sure that I was drinking fairly large quantities of kool aid sweetened with nutrasweet. I can only approximate the amount of nutrasweet beverages I was drinking. There were days that I would drink close to one gallon. Other days maybe only two quarts. I can say with relative confidence, that I at least drank 24 ounces per day, and generally around three quarts. I am a runner and was very conscious about dehydration both from exercise and flying fighter aircraft.

The tremor in my arm continued through December 1983. In January 1984, I was sent on a remote tour to Kunsan Air Base, Republic of Korea. Sometime during the first part of my tour, the tremors stopped. I am not exactly sure the exact date, but can say with assurance that by February 1984 they were gone.

The next episode occurred in June 1984. This was right after I had made a purchase of crystal lite at Osan Air Base. I purchased one or two jars which lasted me a few days. I don't remember if the tremors began immediately, but I do remember having an episode while on crutches from a sprained ankle. My trip to Osan AB was just prior to hurting my ankle the 2nd week in June 1984. My intake was approximately three to four quarts per day.

The tremors appeared again in August 1984 while I was back in the United States on mid-tour leave. My consumption was slightly reduced due to my decrease in running. While on leave I drank kool aid with nutrasweet.

I returned to Kunsan AB after leave and was tremor-free until the end of October 1984. I returned from a deployment to New Zealand and Australia and had a package from home waiting. This package contained kool aid with nutrasweet. I am not sure of the quantity, but my consumption rate was again between three to four quarts per day. My tremors surfaced once again. During this time frame, I had one which was noticeably more severe. My tremors stopped sometime shortly thereafter, and did not return until I returned to Nellis AFB.

After returning from Korea the end of January 1985, I was stationed at Nellis AFB. Once again, I began consuming kool aid with nutrasweet. My intake varied, but normally was between three to three and one-half quarts per day. Sometime in the spring of 1985, I noticed my tremors had gotten worse. Now my left arm would jerk and pull to the left and my left shoulder and neck would also turn to the left. The duration of these episodes were three to five seconds, and still preceded by an aura. I could not relate a specific time of day, personal activity, or whatever to my episodes. They seemed to be grouped, where several would occur within a couple of days followed by some good days. By October 1985, the frequency had increased along with the severity. On 4 October 1985, I had a grand mal seizure, followed by three or so tremor episodes during my three-day stay in the hospital.

I was released from the hospital at Nellis AFB on 7 October 1985. I quit consuming products with nutrasweet or aspartame on 6 October 1985. I did not have any tremors or episodes from that date forward. On 21 October, while being treated at Wilford Hall Medical Center, I was put on dilantin, an anti seizure drug. The 15 days from 6 October 1985 to 21 October 1985 were the longest I had gone without a tremor for the past several months. Today, two years and 22 days later, I have been completely tremor and seizure free.

I would like to point out that I also consumed diet sodas with nutrasweet from the time they were marketed, except for my tour in Korea. My consumption of diet sodas was inconsistent and I have no way of precisely determining the amount, with the exception of that I usually drank one or two cans at work.

Michael A. Collings
MICHAEL A. COLLINGS

Senator **Metzenbaum**. Major Collings, let me make it clear for the record that you are here as an individual; you are not an official representative of the Air Force at this hearing.

Major **Collings**. That is correct, sir.

Senator **Metzenbaum**. As a fighter pilot, you have to keep in top physical shape.

Major **Collings**. Yes, sir.

Senator **Metzenbaum**. And what did you say you run, about five, six miles a day?

Major **Collings**. Not necessarily every day, sir, but probably three to four times a week; plus I went to the gym every other day.

Senator **Metzenbaum**. When you went to Australia in 1984, did your tremors go away?

Major **Collings**. Yes, sir, they did.

Senator **Metzenbaum**. Were you able to get NutraSweet in Australia?

Major **Collings**. No, sir, I was not. I was not able to even get it at Kunsan, which is a remote base there.

Senator **Metzenbaum**. Is there anything else in your medical history that could explain your symptoms?

Major **Collings**. No, sir. The people at Wilford Hall, their final diagnosis, if you will, tried to link it possibly with a car accident that I had in 1973 where I received a bump over my left eye and had several stitches to sew the cut up. But I never lost consciousness in that particular time frame. And they said it could possibly have been from post-head trauma from that accident.

Senator **Metzenbaum**. Did you have any of the normal tests, the CAT scan, the EEG, the MRI?

Major **Collings**. Yes, sir. I had several EEGs; I have had three to four CAT scans and one MRI.

Senator **Metzenbaum**. And anything in those tests to indicate that there was some cause that could be attributed the reason for what has occurred to you?

Major **Collings**. No, sir, there is not.

Senator **Metzenbaum**. And by reason of this situation, you have been unable to be certified to fly any further?

Major **Collings**. That is correct, sir. The day I had my seizure, I was permanently grounded at that time.

Senator **Metzenbaum**. Have the doctors given you any reason for your seizures and your tremors?

Major **Collings**. No, sir. Like I said, their best recollection or diagnosis is possible post-head trauma from my car accident in 1973.

Senator **Metzenbaum**. What makes you think it could be linked to NutraSweet?

Major **Collings**. Well, sir, prior to 1983, I did not drink any; and my tremors started at that particular time. But I would say definitely during my tour in Kunsan, Korea, after I arrived over there, and my tremors went away, I was not drinking or having any type of liquid with NutraSweet or aspartame in it. And each time I did get hold of some, the tremors did appear.

Senator **Metzenbaum**. Every time you were taking the NutraSweet, those were the instances in which you had seizures or tremors?

Major **Collings**. Well, I never had a full seizure, if you will—I am not sure exactly what a doctor would call it, but the tremor that was localized to my left arm and shoulder and where my neck would pull to the left. And also when I had my seizure in October of 1985, the two following weeks I had no tremor at all, and that was prior to being put on the drug Dilantin. And I quit taking aspartame while I was in the hospital, and that was the longest period I had gone tremor-free for several months at that particular time, sir.

Senator **Metzenbaum**. The longest two weeks without aspartame?

Major **Collings**. Yes, sir. I did not have aspartame in that two weeks, and that was the longest period that I had gone tremor-free for the last several months.

Senator **Metzenbaum**. Tremor-free; I see.

I have a summary of your medical record here from the military.

"Major Collings has an idiopathic partial seizure disorder, which is well-controlled on Dilantin. This condition will prevent him from ever returning to flying, which has been his primary duty throughout his Air Force career."

"Idiopathic" means they do not have any pathological reason for the finding; is that correct?

Major **Collings**. Well, sir, I would have to defer that to somebody, but I believe so.

Senator **Metzenbaum**. I think it means they do not know the cause.

Major **Collings**. I believe it does, sir.

Senator **Metzenbaum**. I think the medical term is—maybe Dr. Miller can confirm. Is that a correct understanding, Dr. Miller?

Dr. **Miller**. Yes.

Senator **Metzenbaum**. All right. Thank you.

Thank you very much, Major Collings.

We will next hear from Dr. Alfred Miller, a physician from San Antonio, Texas.

Dr. Miller, in presenting yourself, would you just tell us a little bit about your background as a physician and where you were trained, et cetera?

Dr. **Miller**. Yes. I am very pleased to be here. I trained at medical school in the University of Texas, internship at Mt. Sinai Hospital in Cleveland, and residency training at the Mayo Clinic in Rochester, Minnesota.

I am very pleased to know that someone of your integrity and leadership ability has begun an investigation into a very critical matter regarding the health of this country.

I am in the private practice of medicine in San Antonio, Texas and function as an internist with a sub-specialty in rheumatology. I am not an investigative scientist. The findings that I have noted are those of a clinician. I am not able to confirm the relationship of these findings to NutraSweet, but I would implore you to further investigate NutraSweet using appropriate scientific methods.

In the past several months, I have been seeing patients with what I believe are severe reactions to NutraSweet. To cite a specific example, one of my long-term patients, a female in her sixties, developed severe headaches. These headaches were investigated with all of the various sophisticated medical diagnostic equipment available. However, no specific diagnosis of any organic etiology could be determined. Therefore, it was presumed that the patient had migraine headaches.

This patient was treated with various anti-migraine headache-type medications. However, her life was miserable. She did not respond to any form of medication. Her headaches persisted on a daily basis and prevented her sleeping at night.

After reading an article in the Journal of the American Medical Association regarding the possibility of patients developing headaches secondary to NutraSweet, I phoned my patient and asked her if she was consuming any products with NutraSweet, and at that time, she stated that her husband—a newly-diagnosed diabetic—had been placed on a diet free of sugar and that virtually every food in her house was now a dietetic food, primarily sweetened with NutraSweet. I suggested that the patient completely eliminate NutraSweet from her diet, and refrain from taking any of the anti-headache medications, to observe the effect of NutraSweet abstinence.

Within 24 hours, the patient became headache-free and to this day has not had another headache.

This is only one example of numerous patients who have consulted me in the past several months with either new headaches or exacerbations of old headaches, and in the majority of these instances, by simply removing NutraSweet from their diets, these patients are now able to function on a day-to-day basis without any significant headaches.

I have also had instances of patients who have become agitated and have had temper tantrums without any specific etiology. However, once they have been informed of the possible effect of NutraSweet, and the avoidance of NutraSweet, their mood has returned to normal, and these patients are now living normal, healthy lives.

I am told that last year alone, there were approximately 5.5 million pounds of NutraSweet added to the American diet. Furthermore, I also have read about cases of seizure disorders that have been precipitated by NutraSweet and have been reproduced on rechallenge with NutraSweet.

Potentially, therefore, this is not an innocuous medication that should be placed in the majority of our food products sold in this country, because of the possible potential deleterious effects on the health of this Nation.

As a physician, I have no NutraSweet in my house, and I have encouraged all of my patients with any tendency toward mood disorders and/or headaches to refrain from NutraSweet products. I wonder how many patients are suffering from similar problems without the awareness that I have provided my patients.

I feel compelled to testify before you and present my views. Your Committee's actions, investigations, deliberations will be carefully watched by the American public. And I hope that you come to a reasonable conclusion and inform the American public of the potential dangers of NutraSweet, and perhaps limit its consumption only to diabetics or those in whom caloric restrictions are essential, while allowing others to use NutraSweet only after they are fully aware of its potential toxic effects.

I would also assume that the toxic effects that I have mentioned are only the tip of the iceberg; and should these patients be followed for a longer period of time, I feel that some of these vascular-type headaches may progress to actual strokes with fatal outcomes.

Thank you.

Senator METZENBAUM. Thank you, Dr. Miller.

Dr. Miller, as I understand it, you are an internist with a subspecialty in rheumatology?

Dr. MILLER. Yes.

Senator METZENBAUM. And you are a full professor at the University of Texas?

Dr. MILLER. In San Antonio, I am on the clinical faculty.

Senator METZENBAUM. I think you did mention, Dr. Miller, that you had seen some studies that linked NutraSweet to certain seizures and results. I think those were the studies that actually only raised the possibility but did not actually provide the total linkage. Are we both in agreement on that?

Dr. MILLER. I am referring also to anecdotal type of case histories. In visiting with fellow private physicians, specifically neurologists—just the other day, I was walking down the corridor of my hospital, and a neurologist was telling me about a patient who had seizure disorders, whose blood levels, anti-seizure medications were proper, the patient was under excellent control and then began having additional seizures. A thorough search did not turn up anything except the exposure to NutraSweet. Upon cessation of exposure to NutraSweet, the seizures abated.

So again, I am not a research scientist. May of the things I am reporting are the feelings of a clinical physician in private practice and in visiting with other private physicians.

Senator METZENBAUM. And not having a definite number, but giving us an estimate, how many patients of yours or reports to you from your colleagues in the medical profession, could you tell us, where you or they told the patient to stop using NutraSweet, and suddenly the problem they were experiencing disappeared? Would there be one, twenty, forty?

Dr. MILLER. In my own personal practice, I would say on the order of ten. However, when I visit with other private physicians and discuss this at various medical meetings, I am astounded by how many each of them can enumerate occur in their practice.

Just the other night when I arrived in Washington and went to a relative's home, there was a call waiting for me from a local physician in the Washington, D.C. area, who understood that I was going to testify today. I called this physician, an internist, female, who told me the story about her headaches after drinking a half of a can of diet drinks, diet cola, and that it was such a puzzle, and she was debilitated for so long until she finally made the connection. This is not a layperson, this is a physician.

So anecdotally, there are so many cases. In my own private practice in my office, probably on the order of ten, but numerous others, people who stop me and say, "My 16 year-old was having headaches chewing gum that had NutraSweet, and now that she has stopped chewing it, the headaches have disappeared," because people know that I have some interest in this relationship.

Senator METZENBAUM. Dr. Miller, what compelled you to come forward and testify before this Committee today?

Dr. MILLER. I really felt compelled to encourage additional investigation of this drug. It has become so prevalent in our diet. I think for individuals who have no reaction to it, that is fine. However, for those people who are walking around this country suffering and debilitated, should the investigations prove that there is a relationship, then I think it would be appropriate at least to have a label on these foods that, for susceptible individuals, certain side effects can be expected, so that these people are forewarned.

Senator METZENBAUM. Thank you, Dr. Miller. I think you pretty much make the point of these hearings, and that is that these hearings will not prove the connection, but the reports confirm the need for new tests of safety, and certainly confirm the need for labelling.

Thank you very much. We appreciate your coming all the way from San Antonio.

Our next witness is Mr. Jim Turner, attorney for the Community Nutrition Institute. He has had a long background in this entire area.

Mr. Turner, nice to see you again.

Mr. TURNER. Thank you, Senator. I certainly appreciate this opportunity to be here today. I just have a very few comments to make.

The two case histories that you heard this morning and the presentations of Dr. Miller are very similar to hundreds of such reports that we have received both at the Community Nutrition Institute and the Aspartame Consumer Safety Network and its members.

There are hundreds of stories of individuals who are in one state or another of debilitation who, when they remove NutraSweet from their diet, are able to then function normally and effectively.

There are some basic premises that I believe we need to say in response to the FDA's analysis. First of all, there is a communications gap. The FDA's argument is that there is not the scientifically conclusive connection necessary to demonstrate the cause and effect relationship they need to take regulatory action.

The point that the FDA is making is not that the events are not occurring; the point they are making is that they cannot prove they are occurring. One of the major points they make is that in examining seizure cases, they cannot rule out other possible causes of seizures. The very process they use, however, means that they also are unable to rule out NutraSweet. It is very important to understand that the FDA has not ruled out NutraSweet.

In addition, it is inaccurate to argue that these are not a large number of complaints about a food additive. I would ask that the FDA indicate any other food additive that has received more than 50 or 60 complaints with the possible exception of sulfites, and even that has not received anything like the kind of complaints that have been received on NutraSweet. In fact, this is more of an adverse reaction record than comes in on most drugs for which there are adverse reaction files.

I would also point out that the FDA Commissioner indicated that headaches are listed as nonsignificant side effect. But in fact, within the reporting system that the FDA uses, headaches, particularly debilitating migraine headaches, are included as a serious side effect.

It is a fact that the Aspartame Consumer Safety Network met with the FDA, and we had a very constructive and positive meeting. It was my understanding as we left that meeting that the FDA acknowledged that the system they were using to collect side effects was not working as well as it should. We reported repeated instances of individuals being told by the answering official at the FDA that there is no problem with NutraSweet and taking no more information.

Senator METZENBAUM. Say that again.

Mr. TURNER. We have numerous instances of people calling the FDA and saying, "We feel there is a connection. What information do you have?" and the person who answered the phone that they are speaking to telling them there is no connection between NutraSweet and side effects and not taking any further information.

We have reported this to the FDA and discussed it with them, and I believe it is very important to understand—my understanding when we finished that meeting was they were going to correct that process by having all NutraSweet calls referred to an appropriate official, so that any suggestion that the number of complaints received prior to August of 1987 when we met with the FDA indicates all the calls that were received by FDA is an inaccurate presentation.

Senator METZENBAUM. Can you document that statement for the Committee?

Mr. TURNER. We have individual statements that we can provide for the record, that is correct.

Senator METZENBAUM. And has the FDA followed up?

Mr. TURNER. We are unclear. The Commissioner said this morning that he had undertaken steps to improve that system. However, since the August meeting there have been instances of individuals calling the FDA and then being referred to the AIDS hotline.

Senator METZENBAUM. To the what?

Mr. TURNER. The AIDS hotline. When the AIDS hotline was answered, the individual said, "We are taking the NutraSweet calls because we don't get enough of them now to have an independent hotline for NutraSweet."

Senator METZENBAUM. You have got to be kidding.

Mr. TURNER. I am not kidding. That is an event that occurred. We are still having communications with the FDA to straighten out the collection. The important point is that the collection system is getting a small number of the cases that occur. They are getting a small number of the cases that actually know enough to call the FDA at all.

There are many other people who do not call the FDA. For example, these individuals here have not called the FDA and launched complaints.

Senator METZENBAUM. The Committee will follow up on that inquiry.

Mr. TURNER. Thank you.

Another aspect of the FDA Commissioner's statement is a comment on reproducibility of side effects. The Center for Disease Control report indicated that 28 percent of the people who they looked at, of the first 650 complaints that they received, had stopped taking NutraSweet and then, either purposely or by accident, encountered it again and had the symptomatic reaction once again. That is 28 percent. It was considered to be a major finding by the CDC and one of the most important facts underlying the need for further clinical testing.

With regard to peer review studies, a substantial portion, and I believe, a majority of the studies that NutraSweet approval relies on, did not appear in peer review journals and were not peer reviewed. That is a very important weakness in the record.

I have one final point, and that is that when you do studies where the majority of the research is paid for by industry, it is not the integrity of the scientists that is a problem, and it is not the intentions of anyone involved in the process that is the problem. It is that the system itself becomes skewed in a direction so that certain questions that would be asked by critics are not asked; and in fact, many of the questions that are asked by critics have never even been funded for research.

It is very important that both those who are proponents of an additive and who are critics of an additive have equal resources to do research. That is the only way we can ever sort out whether a product of this kind is effective or not, or safe or not.

Thank you very much.

[The prepared statement of Mr. Turner follows:]

STATEMENT OF JAMES TURNER

My name is James Turner. I am a consumer interest attorney from Washington D.C. I am also the author of **The Chemical Feast: The Nader Report on the Food and Drug Administration** and **Making Your Own Baby Food**. I represent the Community Nutrition Institute and the Aspartame Consumer Safety Network in various legal challenges to the approval of aspartame.

My first encounter with aspartame was in 1971 when Dr. John Olney of Washington University in St. Louis, with whom I worked on several food additive issues, informed me that aspartic acid, a component of the then brand new sweetener aspartame, had caused lesions (holes) in the brains of mice he was testing. Both Dr. Olney and I met with representatives of Searle prior to the FDA approval in 1974, but they did not feel that these animal studies raised any health problems.

Dr. Olney and I objected to the 1974 approval based on Dr. Olney's mouse study, another study in which monkeys consuming aspartame had epileptic seizures, and what I alleged to be the poor quality of several other Searle studies. FDA granted our request for a hearing and a years' long battle ensued.

In 1981, the FDA commissioner overturned the decision of a Public Board of Inquiry that more studies be undertaken on the possibility that aspartame might be cancer-causing, and in 1983 FDA extended approval to soft drinks. With the approval of aspartame for soft drinks, followed by reports from several thousand consumers that they had suffered damage from aspartame, a major public controversy ensued.

In June 1983, a month before FDA approved the addition of aspartame to soft drinks, the National Soft Drink Association wrote the FDA Commissioner warning that aspartame breaks down in unexplained ways in warmer climates. The Assocaiton said:

> The more persistent, warmer temperatures in some parts of the U.S. will result in more extensive aspartame breakdown. The current petition clearly shows (in Appendix 2) this more complete breakdown of aspartame at temperatures above 30 degrees C. Additionally, the petition indicates inabilty to account for what has happened to as much as 30% of the sweetener, despite having analyzed for compounds expected in the usual breakdown pathways.

In responding to questions about breakdown product safety the Commissioner said:

> The agency also concludes that the allegation that all possible reaction products have not been tested for safety is not a tenable issue in terms of regulatory food additive safety evaluation. Such a requirement for the demonstration of safety would necessitate an unlimited amount of experimental data. [48 FR 142 p. 31381]

The Food Drug and Cometic Act requires [21 USC 348(c)(5)] that the FDA consider:

> (A) The probable consumption of the additive and of any substance formed in or on food because of the use of the additive;
> (B) The cumulative effect of such additive on the diet of man or animals, taking into account any chemically or phamacologically related substance or substances in such diet. [46 FR 142 p.38287]

Forgoing identification and testing of the 30% of the aspartame that disappears at product temperatures exceeding 80 degress F may be prudent or defensible. I suspect it is neither. In any case, consumers and legislators need to understand that "safety" as defined in the food and drug law does not apply to 30% of the aspartame additive.

This is just one specific aspect of aspartame's approval that raises doubts about its asserted "safety". The tests that suggested a cancer-causing possibility to the Public Board of Inquiry have not been convincingly rebutted. The test in the 1974 petition in which aspartame caused seizures in monkeys, and which was the subject of a request for a Grand Jury investigation, has yet to be adequately explained.

Raising the acceptable daily intake to make room for soft drinks; overruling official recommendations that marketing be delayed; arguing that withholding aspartame from soft drinks "provides an extra cushion for purposes of Searle's current petition" and then relying on the same data to add aspartame to soft drinks; all undermine confidence in the soundness of the science relied on by FDA to approve aspartame.

It will be a long time before the aspartame controversy goes away. But there are currently many other food additives waiting in the wings, new sweeteners, salt and fat substitutes and others which hopefully can be handled in a way that builds rather than undermines public confidence. Setting aside for the moment the specific controversies about aspartame, I hope we can all agree that any actions that can build a general confidence in the food safety decisions of the FDA will help us all.

With this idea in mind I think there are three general areas that need attention: the scientific testing done before an additive is approved; the manner in which doubts, limitations and possible dangers are communicated to the public through labeling and advertising; and the manner in which an additive, once approved for the market, is monitored for possible dangers.

The following proposals are suggestions made to start a dialogue, not to present an inflexible position. Much of the thinking that has gone into them was done by me when I served as a founding board member of the Food Safety Council -- a group made up of thirty-five food companies interested in food safety. It had a board membership which was fifty percent from the food industry and fifty percent public. I beleive that the FSC was an important effort, and much of its work will prove relevant to the emerging food safety debate.

With regard to testing prior to approval it appears to me that there is one central problem. Individual scientists cannot do their best and most objective work when they are financially beholden to the companies who stand to make hundreds of millions, or even billions of dollars based on the outcome of their research. (One Searle-supported aspartame researcher is reported to have received $1.3 million for his laboratory.)

It is not necessarily a matter of conscious objectivity that poses the problem. Nor is it the problem that enough money will convince a scientist to say that an obviously dangerous additive should be treated as safe. The problem is that in the emerging scientific areas such as brain chemistry, scientific decisions are often a matter of subtle judgments.

It is naive to argue that a subtle observation on the outcome of which rides over a million dollars of laboratory research money can be made objectively even by the most strong-willed.

Indeed, the whole basis of the American system is the opposite -- give a scientist enough money and he will find what you ask him to find -- a cure for cancer, an efficient fuel, a spaceship.

Entreprenuerial science is sound when you are looking for cures, products, breakthroughs. It does not work well, as currently organized, when you are looking for weaknesses in products, putting brakes on the marketing team, or in other ways limiting money-making potential.

My suggestion is to get the entreprenuerial spirit working for safety. The FDA, or another properly designated agency could certify a series of laboratories as capable of doing the various kinds of testing necessary for product approval -- the agency Red Book sets these out now.

Today when a company does the designated test, it hires and pays the laboratories directly. I propose that this relationship be replaced by having the company go to the FDA with its new additive, and the FDA would then assign on a random basis the test required to the previously certified laboratories. The companies would pay the FDA, who would then pay the laboratories.

With regard to information to the public, it is necessary to recognize as Dick Hall, Research Vice President of the McCormmick Company said at one of the final meetings of the Food Safety Council, food safety has become personal, subjective and relative. We can no longer, if we ever did, deprive the whole population of some substance just because some small part of the population will be harmed by it.

On the other hand, it is not proper to lead the entire population to believe that an additive will hurt no one merely because it does not hurt everyone. In this sitution it is absolutely essential that every single sub-group of the population that might be at risk from an additive be told of that possibility -- as much as possible through labeling and advertising warnings. If the full information cannot fit into ads or onto labels then the ads and labels need to tell consumers where to get the detailed information.

Finally, once a substance reaches the market it should not be treated as sacrosanct. It must be recognized that over time a substance that we know harms people will continue to harm people, whereas a substance that we believe might not harm people sometimes turns out to be harmful. My suggestion is that we account for this possibility by creating a rigorous post-marketing surveillance system. This can be accomplished by putting in place a prospective epidemiologic system -- by identifying a properly constituted sample of individuals who use the product and following them for five, ten, twenty or more years so that as soon as there is any suggestion of harm to the population it can be discovered.

The proposals I am presenting here are meant to strike a balance between those consumers that want to consume a large number and wide variety of food additives for various purposes, and those (not necessarily totally different consumers) who may face the possiblity of harm from an additive that poses no danger to many other people.

If the standard of food safety is that a substance that harms some people but not all people is going to be allowed on the market, then special polices need to be adopted that will protect those at risk.

Thank-you for the opportunity to testify here today.

Senator **Metzenbaum**. Mr. Turner, how do you feel about the way scientific research is conducted, generally, on food additives?

Mr. **Turner**. The research process on food additives is a weak process. Virtually all the FDA does is summary reviews of studies done by other scientists, and those studies are invariably submitted by industry, and they are presented as a trial brief, an argument why the substance should be allowed in the food supply, not as a balanced analysis of whether or not the substance is safe.

Senator **Metzenbaum**. Do you believe the key tests that were used in this instance for NutraSweet's approval were scientifically credible?

Mr. **Turner**. At the very least, they are highly controversial, and in particular one set is of great importance. There are clinical tests that were referred to by the Commissioner today that indicated why he could reduce the safety factor from 100 to 40. These clinical tests were submitted by the Bureau of Foods to the Bureau of Drugs for evaluation. The Bureau of Drugs routinely does clinical testing; the Bureau of Foods does not. The Bureau of Drugs reviewed those clinical tests and found them to be unacceptable to be relied on for regulatory purposes. They were returned to the Bureau of Foods with explanations about how to conduct proper clinical tests; the Bureau of Foods decided not to conduct those tests because they were not required for food additives.

[Information supplied follows:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. C. J. Kokosi
Division of Toxicology (BF-152)

DATE: SEP 12 1973

FROM : Supervisory Medical Officer
Division of Metabolic and Endocrine Drug Products (BD-130)

SUBJECT: Aspartame - A New Artificial Sweetener FAP NO. 3A 2885

The clinical reports you forwarded have been reviewed by Martha M. Freeman, M.D. of this Division, and a copy is attached for your permanent file as requested.

We regret that the information provided is inadequate to permit a scientific evaluation of the clinical safety of Aspartame. The specific deficiencies are indicated in the attached review.

Bernard
Berna

Attachment

W19 1

Aspartame
Artificial Sweetener

August 20, 1973

MEDICAL REVIEW OF CLINICAL SAFETY STUDIES
FAP No. 3A2885

Sponsor: Searle Laboratories
Division of G. D. Searle & Company
P.O. Box 5110
Chicago, Illinois 60680

Product: Aspartame - PROTID

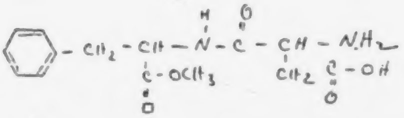
Category: Artificial Sweetener

a. 180 x as sweet as sugar (comp. saccharine 500 x and cyclamate 40 x as sweet as sugar).

b. 0.5% caloric value of equivalent sweetening.

Chemistry: Methyl ester of aspartic acid - phenylalanine dipeptide

Formula:



L-aspartyl-L-phenylalanine methyl ester

Molecular Equivalents:

Aspartame 1.78 gm = 1.0 gm phenylalanine
Aspartame 0.6 gm = 0.34 gm phenylalanine

Proposed Use:

Sugar substitute; "of special value to persons with metabolic disorders that limit the use of sucrose."

Dosage:

Anticipated intake - 0.6 gm/day as food additive (12 mg/kg/day for a 50 Kg person).

Investigated: a) 1.8-8.1 gm/day (36-165 mg/kg/day) in t.i.d. dosage x 6-27 wks. (=3-13 x anticipated daily intake).

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Aug. 20, 1973

b) 39.5-58 mg/kg/day in normal children.

c) 34 mg/kg/day in PKU patients.

Formulations Used: a) Capsules 0.2, 0.3 gms. t.i.d. with meals.

b) Food additive in gelatin, pudding, soft drinks, etc. for normal children.

c) Powder in orange juice to PKU children.

Material Reviewed: Clinical Studies - desk copies of vols. 1, 2, 3.

Purpose of Review:

Dr. Kokoski, Division of Toxicology BF-152 request SD opinion as to whether safety problems might be anticipated should this sweetener be marketed for general use.

Summary:

Summaries of 10 completed studies were submitted (the majority of which were BD pl controlled) in normal adults and children; in healthy obese adults; in diabetic adults (insulin-and non-insulin dependent); in adult PKU heterozygotes (i.e., parents of PKU children); and SD studies of PKU children compared with molecular equiv. doses of phenylalanine.

Monitoring included the usual hematologic, prothrombin, ~~rival~~ renal and liver function, plus T_4, phenylalanine and tyrosive levels, methanol levels (method measured 3 μg/ml), serum lipids, glucose and insulin levels post-glucose-loading; oph-thalmologic; EKG in diabetics; EEG in PKU heterozygotes.

Dosage (except otherwise specified) was 1.8 incr. to 8.1 gm/day over a 6 wk. period for "short term"; and 1.8 gm/day x 21 wks. for "long term" tolerance - administered in capsules in t.i.d. divided dosage.

NOTE:

No curriculum vitae information nor protocols were provided. Reports consist of narrative summaries and tabulations of the means ± SE for each laboratory parameter. No information is submitted regarding the identity of the reporting laboratories, methods used (rare exceptions) nor normal values. The units reported for T_4 and serum insulin cannot be verified at the time of this review. Reported alk ptse values in King Armstrong units appear to be in error.

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1. Dr. Kenneth J. Langlois conducted a 6 wk. DB pl study in 69 normal adults at 1.3 increased to 3.1 mg/day. Fifty continued into the 21 wk. study with 17 additional normal subjects at 1.8 gm/day, which was carried out by Gunther Frey, M.D.

   Results reports no statistically significant drug related changes in lab parameters; no detectable methanol levels in 8 AM blood and urine specimens (method used detected levels 3 mg/ml compared to reported normal of 1 mg/ml). Side effects were mild, more frequent in the drug subjects and at the higher doses: gas, loose stools, anorexia or increased appetite, rash (3), swelling (2).

2. Drs. Richard Hoffman, Thomas McGinn and Francis Romano studied the drug in healthy obese adults (20% over ideal) aged 21-70 yrs., using DB pl design in 95 subjects at 1.8 incr. to 8.1 mg/day x 6 wks., and in 105 subjects at 1.8 gm/day x 21 wks. (which included 69 of the subjects from the 6 wk. study).

   Results included 11 drop-outs in the high dose portion due to drug bulk (27 capsules!), and 9 in the long-term study. Mean weight changes included 3 and 6 lb. losses for drug and placebo groups in the short term; and plus 5 lbs. and minus 5 lbs., respectively in the long-term. Two were dropped because of pregnancy. (Continued surveillance showed "no ill effects." There were no statistically significant drug related changes in laboratory parameters. Mild GI side effect were more frequent in the drug subjects.

   Comment - Age stratification of side effects would be of some interest.

3. Dr. Gunther Frey studied the drug in 126 normal children and adolescents aged 2-20 yrs. in DB design x 90 days, using sucrose controls. Aspartame 39.5-58 mg/kg/day was supplied in dietary supplements, e.g. gelatin, pudding, soft drinks, packets for use on cereal, etc. (Older subjects also received 1 cap. of 0.2 gm. t.i.d.).

   Results show no drop-outs. Sponsor's analysis by 5 age groups showed no drug related changes in any parameter. Negative methanol levels were reported in the 33 subjects listed (fasting specimens!). Mild GI side effects appeared similar in both groups.

4. Results were pooled from 3 separate DB pl studies in 65 PKU heterozygotes (natural parents of PKU children) by Drs. Richard Koch, R. Peterson, and Charles Scriver. Dosage for the 6 wk. portion was 0.6 increased to 8.1 gm/day (equiv. to phenylalanine 0.34 incr. to 4.55 gm/day); and 1.8 gm/day x 21 wks. in 52 subjects for the uninterrupted long term ~~excretion~~ extension.

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to above studies and also included EEG in

[illegible]atistically significant drug related differences in the lab parameters, including PA and T levels. No explanation was offered for GTT 150 mg% at 1/2 hr for drug and placebo groups.

Sponsor concluded that PKU heterozygotes are at no greater risk of excess phenylalanine levels from Aspartame than are normal subjects.

5. Drs. Richard Koch and Kenneth Shaw did comparative phenylalanine blood level studies in 2 PKU (2 M aged 14) and 2 normal (M 12, F 15) adolescents, using single loading doses of Aspartame 35 mg/Kg in orange juice, followed by molecular equivalent doses of L-phenylalanine 19 mg/kg.

   PKU homozygotes are characterized by congenital absence of phenylalanine hydroxylase and are therefore unable to convert excess phenylalanine (PA) to tyrosine. This results in the accumulation of abnormal metabolites which are damaging to the CNS. Strict limitation of PA intake is essential during infancy and childhood of PKU subjects in order to prevent severe mental retardation. The optimum age for discontinuing the PA dietary restriction has not been determined, but is thought to be around 6-8 yrs. The restricted diet permits 20-30 mg/kg/day compared to the normal 50-200 mg/kg/day intake. "Liberalized" diets for older PKU children contain 50-100 mg/kg/day.

   Results - These amounts of PA when added to the dietary intake resulted in the permitted amount of PA for the subject on the liberalized diet, but greatly exceeded the amount permitted by the restricted diet, with equivocal increases of urinary metabolites.

   No data are provided on PA and T blood levels. The sponsor claims no significant rise in either.

   Comment - It is not feasible to extrapolate results of such single dose testing to the likely conditions of use of Aspartame as an artificial sweetener.

   Similar studies in 21 normal adolescents (12 yr. M, 15 yr. F) resulted in no metabolic abnormalities.

6. Dr. Sheldon Bleichar and Dr. Sol B. Stern each conducted studies in 77 insulin-dependent and 69 non-insulin dependent diabetics at

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doses 1.8 gm/day x 90 days, using DB placebo controls. Pooled results were as follows:

A. Insulin - dependent: Seventy seven patients (39 A, 38 P) (+ 13 drop-outs). No drug related changes in: degree of diabetic control (i.e., FBS 150 mg%), weight changes, blood pressure, pulse (mean averages), clinical laboratory parameters; plasma PA & T levels, ophthalmologic, EKG. Serum lipid changes as follows:

	Aspartame	Placebo
Cholesterol (elevated)	4 decr.	2 decr.
(normal)	4 incr.	
Triglyceride (elevated)	4/8 decr.	

Adverse:

(1) Drop-out at 11 wks. dt. mastectomy for adenocarcinoma (considered non-drug related).

(2) One "stroke" at 8 wks. in 72 yr. F with atherosclerotic heart disease. FBS baseline 193 mg% incr. to 293 mg% at 8 wks. "Later expired."

(3) One had 2 abortions during the study.

(4) Side effects included mild G.I. symptoms in 2; and symptom of insulin reaction, mild hypoglycemia in 6 drug and 6 pl subjects.

B. Non-insulin dependent: Sixty nine subjects (36 A, 33 pl) + 6 drop-outs, (on concomitant diet and/or drugs).

No significant drug related changes in: Degree of diabetic control weight change, vital signs, liver and renal function, PA and T levels ophthal, EKG.

Adverse effects:

(1) One patient became pregnant and dropped from study at 11th wk. of study (monthly follow-up continued, and the infant will be monitored for PA levels and mental development until 3 yrs.

(2) One dropped at 11th study week due to surgery for reticulum cell CA of stomach ("gastric lymphoma") which was considered non-drug-related.

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Note: B. H. Wagner, M.D. Cl. Prof. Pathology, College of Physicians and Surgeons reviewed stomach sections from 2 yr. rat studies and found no abnormalities in gastric or adjacent lymphoid tissues).

Summary:

A food additive petition has been submitted for Aspartame (methyl ester of dipeptide of aspartic acid and phenylalanine) as an artificial sweetener (180 x as sweet as sugar, with 0.5% the caloric value for comparable sweetening).

It is proposed for use as a sugar substitute "of special value to persons with metabolic disorders that limit the use of sucrose." The anticipated intake is 0.6 gm/day (12 mg/kg/day for a 50 kg individual).

Extensive clinical safety studies "were conducted under the food additive petition with the awareness and encouragement of the FDA" in normal adults and children, in populations with metabolic disorders who would be likely to use aspartame (obesity; diabetes); and in metabolic disorders which might be at risk - e.g., abnormalities of phenylalanine metabolism: - PKU patients and potentially pregnant PKU heterozygotes (fetal CNS is vulnerable to elevated maternal PA levels).

The BF Division of Toxicology requested a medical evaluation and opinion as to whether safety problems might be anticipated if the product is marketed for general use by the public.

NOTE:

Although it was stated that studies were also performed with diketopiperazine an impurity which results from acid hydrolysis of Aspartame, no data are provided on this product.

Dr. Kolosky (BF-152) indicated per telephone (8-17-73) that particular areas of concern are:

1. The metabolism of the mythyl group to methanol.
2. The report of possible brain tumors in U.S. rat studies but not in Canadian studies.
3. Possible metabolism to nitrosamine compounds.

The sponsor claims that "there is no potential hazard (from methanol), even if massive amounts are consumed"... Also, "if all sugar in the normal diet is replaced by Aspartame, it would add 2% to the phenylalanine content of the diet."

[illegible]

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Evaluation:

The information provided is inadequate to permit an evaluation of potential toxicity of Aspartame because of the following deficiencies:

Chemistry - No information is provided other than formulae for Aspartame and its diketo-piperazine.

Pharmacology - Reference is made to 2 yr. rat studies, but no data are provided on acute or chronic toxicity.

Clinical - No protocols nor curriculum vitae information are provided for the 10 completed clinical studies. Results are reported in narrative summary form, and tabulations of mean average values only. No information is given as to the identity of the reporting labs, methodology (except rarely), or normal values. (Reported units for several parameters cannot be verified at this time).

No pharmacokinetic data are provided on absorption, excretion, metabolism, half-life; nor bioavailability of capsule vs. food-additive administration.

Conclusions:

1. The administration of Aspartame, as reported in these studies at high dosage levels for prolonged periods, constitutes clinical investigational use of a new drug substance.
2. The information submitted for our review is inadequate to permit a scientific evaluation of clinical safety.

Recommendations:

1. An IND should be filed, to include all required manufacturing controls, pharmacology and clinical information.
2. Marketing for use as a sweetening agent should be contingent upon satisfactory demonstration of clinical safety of the compound.
3. See suggested Memo (attached) from ~~E. A. Ortiz~~ George Liang to J. Richard Crout, Director, Bureau of Drugs.

cc:
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Dup
OSE/BD-100
MED/BD-130
Chemist/BD-130
Pharmacologist/BD-130
Pharmacology/BD-130
MMFreeman/jmb/9-7-73
CJ Kokoski - BF-152
W D'Aguanno - BD-152

9/12/73

Martha M. Freeman
Martha M. Freeman, M.D.

MEMORANDUM

DEPARTMENT OF

FOOD

CG70

[illegible] Clinical studies

TO : Associate Commissioner for Compliance

DATE:

Did this memo issue?
NO - [illegible] Rank 1/11/74

FROM : Acting Director
Bureau of Drugs

SUBJECT: FDA Responsibility for Safety Evaluation of Proposed New Sugar Substitutes - ACTION MEMORANDUM

ISSUE

The Bureau of Drugs recommends that the Associate Commissioner for Compliance institute procedures to require that safety evaluations of proposed new sugar substitutes be conducted as Phase I studies under the Investigational New Drug (IND) Regulations.

BACKGROUND AND DISCUSSION

The Bureau of Drugs has been requested by the Bureau of Foods to provide support in the medical review of completed clinical studies to evaluate the safety of an artificial sweetener.

The Bureau of Foods, Division of Toxicology, recently requested a Bureau of Drugs medical review of clinical safety studies of Aspartame (Tab A) a proposed new sweetening agent. The studies were completed under the FAP 3A-2885. The Bureau of Drugs was also requested to provide medical opinion as to whether a safety problem was anticipated if the product was marketed for general use by the public.

The information submitted for review was limited to narrative clinical summaries and tabulated mean values of laboratory studies. No protocols, manufacturing controls information, or pre-clinical data were provided. Such deficiencies in each area of required information precluded a scientific evaluation of the clinical safety of this product.

In view of the current situation regarding saccharin and the cyclamates, FDA may well anticipate active development by the industry of new products to be marketed as sweetening agents.

The potentially serious and far reaching influence of the general issue regarding the safety of artificial sweeteners, requires Bureau of Drugs input and involvement at the early design stages of studies contemplated by the firms sponsoring food additives through the Food Additives Petition (FAP) regulations. This is preferable to the "after-the-fact" involvement of the Bureau of Drugs which is the current practice.

Clinical safety testing of these food additive products is tantamount to investigational new drug use. In view of high dose, and long term administration, we believe such trials should be conducted under the IND regulations, including the acquisition of informed consent from the clinical subjects. Subsequent processing as a food additive should then be continued in the Bureau of Foods under the FAP regulations.

A recent and voluntary precedent for initial IND submission of proposed sweetening agents has been set by industry. IND 9062, for Tetrazole was submitted by Eli Lilly & Co., on August 21, 1972.

A less favorable option would be for the Bureau of Foods to request cooperation from the Bureau of Drugs upon receipt of proposed Food Additive Petition to enable input from the Bureau at the onset of the proposal. The option may be less desirable from a logistics point of view since it entails the inter-bureau transportation of files and personnel in order to provide the required cooperative review during the planning and review stages of the clinical trial.

A third "option" would be to recommend to the Bureau of Foods that the regulations (Tab B - para. 121.51) be amended to provide for more definitive requirements for conducting studies designed to evaluate the safety of food additives for human use. We believe this to be yet less desirable than the above proposals since this may require the establishment of a medical staff in the Bureau of Foods which essentially would duplicate staff review procedures, and adequate regulations already in existence and of proven effectiveness within the Bureau of Drugs.

RECOMMENDATION

In view of the above alternatives, we recommend that this proposal be endorsed to state that studies designed to evaluate clinical safety of artificial sweeteners, classified as food additives, be conducted under the Investigational New Drug Regulations.

J. Richard Crout, M.D.

Enclosure: Tab A - Medical Review of Clinical Studies - FAP 3A-2885
Tab B - Food Additive Regulations, Part 121

cc20

Decision

1. Clinical trials to demonstrate safety of artificial sweeteners, whether food additives or not, are to be performed under the IND Procedures.

Approved ________________ Disapproved ____________________ Date ________

Prepared by: BD-130, MMFreeman, M.D., JASantangelo, TMChin, X33490

Senator METZENBAUM. Thank you very much.

We appreciate the witnesses' testimony. It has been very helpful to us, and we appreciate your being with us today.

Senator Hatch?

Senator HATCH. Thank you, Mr. Chairman.

Mr. Turner, since 1974, how many objections or petitions alleging that aspartame is unsafe have you filed with the FDA or any other Federal regulatory agency?

Mr. TURNER. Three.

Senator HATCH. Three. In August 1974, did you file objections with FDA and a request for a hearing regarding the approval for "dry" uses of aspartame?

Mr. TURNER. That is correct. And on the basis of our petition, they did grant a public hearing.

Senator HATCH. All right. Did you testify during that hearing that aspartame causes brain damage and mental retardation?

Mr. TURNER. I did not, no.

Senator HATCH. You did not. What was the outcome of that hearing?

Mr. TURNER. The public board of inquiry ruled that aspartame should not be marketed because further testing needed to be undertaken.

Senator HATCH. Did the board reject your contentions at that time or your position?

Mr. TURNER. My contention?

Senator HATCH. Yes.

Mr. TURNER. My contention was a general contention that it had not been shown to be safe, and that was adopted by the board.

Senator HATCH. Your position was adopted by the board, you say, at that time?

Mr. TURNER. My position was that the tests did not establish safety. The board concluded that with regard to brain tumors, that safety had not been established, and the substance should not be marketed.

Senator HATCH. In August 1975, in a telephone conversation with the then general counsel of the FDA, did you raise the issue of uterine polyps in connection with aspartame?

Mr. TURNER. I called attention to the fact that the uterine polyps existed, and I think that the agency had already been aware of that.

Senator HATCH. So you raised the issue, is what I am saying.

Mr. TURNER. Yes.

Senator HATCH. Okay.

Mr. TURNER. Well, I acknowledged that the issue had been raised, yes.

Senator HATCH. Sure. In the 12 years since you made that charge, have there been any scientific study or studies substantiating the allegations you raised?

Mr. TURNER. Well, that was my point. I did not make a charge. I said that there was a study showing that there were uterine polyps; and in fact, they were there, there were uterine polyps; they were found by several pathology laboratories. The answer they gave, however, was that they were not pre-cancerous uterine polyps.

Senator HATCH. Okay. Other than that study, in the 12 years subsequent to that time have there been any scientific studies substantiating those allegations, to your knowledge?

Mr. TURNER. Well, following my phone call, there were five pathology laboratories that confirmed the uterine polyps. The only issue was whether they were cancerous.

Senator HATCH. I am not talking about confirmation at that time. I am talking about any studies that were subsequent to that time.

Mr. TURNER. I think it is a given. I do not think there is any issue about that.

Senator HATCH. Have you ever raised the issue regarding the approval of aspartame when used in combination with monosodium glutamate, and if so, what was the outcome?

Mr. TURNER. I did not raise the issue again. Dr. John Olney, who was a separate person who was raising issues at the same time, did raise the issue about the combination. The board concluded that the evidence at that time, based on their assumption of the threshold level of NutraSweet or aspartame that would get into the bloodstream, that they did not see that that was going to make a problem.

Senator HATCH. Okay. In 1983, when the FDA approved aspartame for use in carbonated beverages, did you again ask for a hearing based on the possibility of brain damage, the potential for mental retardation, brain lesions, the toxicity of breakdown products of aspartame, and the toxicity of methanol; and if so, what was the outcome of the FDA's review of your particular request at that time?

Mr. TURNER. Well, we requested a hearing on the understanding that we believed was in the record, that there was going to be a hearing on diet sodas that was distinct from the hearing on dry foods. The FDA rejected that request.

Senator HATCH. All right. Have you ever appealed any of those cases, and if so, to what level, and what was the outcome?

Mr. TURNER. We did appeal to the United States Court of Appeals, and they ruled that the dry foods petition could be used to support safety for soft drinks. And they ruled that we were not entitled to a hearing. We appealed that—we filed for cert to the Supreme Court and were denied a hearing.

Senator HATCH. Your appeal was denied?

Mr. TURNER. That is right.

Senator HATCH. Finally, did you file a petition with the FDA in 1986, seeking the ban of aspartame because it causes seizures?

Mr. TURNER. That is correct.

Senator HATCH. What was the outcome?

Mr. TURNER. Well, we filed for seizures and eye damage.

Senator HATCH. What was the outcome of that?

Mr. TURNER. The FDA denied that. We are in the appeals court now. We filed our briefs last Friday. We believe we have a stronger case today than we did the last time.

Senator HATCH. Mr. Chairman, let me just make one request, and that is, let's allow the FDA to respond to Mr. Turner's concerns. I think we should do that and leave the record open so that he can respond.

Senator **Metzenbaum**. I think Mr. Turner and the FDA have been responding to each other over quite a period of time.

Senator **Hatch**. But I mean for our record, so that we will have the responses in the record. Is that all right?

Senator **Metzenbaum**. No problem, no problem at all.

Senator **Hatch**. Okay. Thank you. That is all I have.

Senator **Metzenbaum**. Thank you very much, gentlemen. We do appreciate your testimony. It has been very helpful.

Our next panel consists of Dr. Richard Wurtman, Dr. Louis J. Elsas, Dr. William M. Pardridge, Dr. Peter Dews, and Dr. John Fernstrom.

Good morning, gentlemen. You know about our five-minute rule.

Dr. Wurtman, nice to see you again, sir. Please proceed.

STATEMENTS OF DR. RICHARD J. WURTMAN, DIRECTOR, CLINICAL RESEARCH CENTER, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, BOSTON, MA; DR. LOUIS J. ELSAS II, DIRECTOR, DIVISION OF MEDICAL GENETICS, PROFESSOR OF PEDIATRICS, EMORY UNIVERSITY, ATLANTA, GA; DR. WILLIAM M. PARDRIDGE, PROFESSOR OF MEDICINE, DIVISION OF ENDOCRINOLOGY AND BRAIN RESEARCH INSTITUTE, BLOOD-BRAIN BARRIER LABORATORY, UNIVERSITY OF CALIFORNIA, LOS ANGELES, CA; DR. PETER B. DEWS, PROFESSOR OF PSYCHOLOGY AND PSYCHOBIOLOGY, HARVARD MEDICAL SCHOOL, BOSTON, MA, AND DR. JOHN D. FERNSTROM, DEPARTMENTS OF PSYCHIATRY AND BEHAVIORAL NEUROSCIENCE, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA

Dr. **Wurtman**. Thank you, sir.

First, may I say to you and to Senator Hatch, I am honored to be here, and I hope that these comments will be of some use.

I am a physician; I am a professor at the joint Harvard/MIT Medical School. I am the Director of the NIH-funded Clinical Research Center at MIT, and I am also a basic scientist. I have been responsible as thesis advisor for the training for about 40 students who took their Ph.D.'s, and I am delighted to see one my students, Dr. Fernstrom, on the panel here with me; also, about 70 postdoctoral fellows.

My laboratory at MIT, I think can be said to have pretty much discovered the short term effects of nutrients on the brain about 15 years ago. Since that time, we have published about 400 papers in peer-reviewed scientific journals on this topic, and I have written about eight books on it.

That is the basis of my interest in aspartame. Aspartame contains amino acids. Any time people take any amino acid, and it might affect the brain, that is my business.

In 1981, I testified in favor of aspartame at the Board of Inquiry. The concern that I addressed then was the aspartic acid part of aspartame. I thought then, and I still think, the aspartic acid is no problem. But about 1983, I became concerned about the phenylalanine in the aspartame, especially when I knew that aspartame would be added to soft drinks, because my prior experience as a consultant and advisor to ILSI's Caffeine Committee led me to know that people drink a lot of soft drinks, and so I thought the consumption of aspartame might go up.

Moreover, the work of my own laboratory had shown that the effect of taking phenylalanine in any form on the brain would be enhanced if it were consumed along with a dietary carbohydrate.

I see many of my thin, robust MIT students drinking a Diet Coke while they eat cookies. I suspect that the majority of aspartame users are not fat people, and are not diabetics. We do not put it in that part of the supermarket, right? So my concern was of the possible use of large amounts of aspartame by the Major, who we just heard.

I made some scientific postulates about what aspartame might do to the body, about five postulates. Every one of them was denied hotly by the Bureau of Foods when they were first made. I think they have come around on four of them now.

What are they?

First, the consumption of aspartame is different from the consumption of protein. All phenylalanine is not equal. The phenylalanine in aspartame is consumed without other neutral amino acids, and so it has a major effect on plasma amino acid pattern, which you do not see with eating protein.

Secondly, this effect on the plasma would cause changes in brain phenylalanine and tyrosine.

Thirdly, this would affect the production of neurotransmitters.

Fourthly, this would affect brain function in rats. And the kinds of functions, by the way, are important to note. The neurotransmitters that aspartame and phenylalanine affect are not yes/no type transmitters. They do not cause things by themselves. They modulate things. I would not expect aspartame to cause seizures. What might happen is it might lower the threshold to some other, nondiagnosed, idiopathic mechanism causing the seizures or the headaches.

Fifthly, I postulated based on these rat studies that there might be some effects of aspartame in some people, susceptible people, who took large amounts of it. The FDA's initial response to this was the head of the Bureau of Foods saying this is silly; people eat a lot of protein, there is a lot of phenylalanine in protein. I think they have changed, but after this morning, I am not completely sure.

Now, we try to do a lot of research on this. I have been one of the fortunate few people that I know of who has received an NIH grant to do research on aspartame. But very few investigators have received such grants, and very few have applied, because the response understandably has been when the NIH has very few dollars to put into research, why should it put the money into doing basically toxicology studies on some monopoly product.

I think we need a different mechanism for supporting the large numbers of university investigators who I believe would like to do research on this. I do not know what the mechanism should be.

Now, I have attempted to work with industry off and on in my own studies on aspartame. At the time of the 1985 sweetener hearings, at which I spoke against aspartame, I was, as I mentioned, a consultant to the NutraSweet Company. I think that whether or not I have been a consultant or received research funds from the company, as I think you can judge, has had precious little effect on the nature of what I have said. One says the same thing in all circumstances.

I quit at the end of that year because I became convinced that the personnel with whom I was dealing were not really interested in exploring the toxicity of NutraSweet. I have been invited several times to go back as a consultant, and I have refused to do so. I do have some research grants from the NutraSweet Company to study basic science aspects of phenylalanine, but I have not accepted any funds to do toxicity studies, safety studies. I do not think that would be proper.

I have two concerns now. One is with the safety of aspartame for some people some of the time—people like the Major, if you will—and I know other members of this panel will address those questions. So I would like to turn my attention in the time that is left to the other thing that concerns me, namely, what can we learn from this experience.

Aspartame, as you know, is the first new food additive, widely used, to come onto the market in about four decades. That, by the way, is why it is the most studied food additive. It is also the only food additive.

Okay. We are going to be seeing more food additives, artificial sweeteners, cholesterol substitutes, et cetera. I think we have to change the law and the way that new food additives are regulated. And I would like to, if I may, make some suggestions as to what I would hope Congress might do.

First, I think there should be standing advisory committees that determine the need for certain types of food additives—should there be artificial sweeteners, and if so, what criteria should we use to judge the efficacy of this compound, or this compound or this compound. This is what we do with over-the-counter drugs all the time.

It has been said that aspartame is useful to diabetics. I do not know of a single study that has shown that aspartame has any effect whatsoever on the clinical management of diabetics. There are no data showing that aspartame is useful in weight loss. A recent study done in Boston showed that at least it did not interfere negatively with the effects of dieting.

Anyway, I think there should be committees that define needs and set up criteria as we have for over-the-counter drugs.

Second, I think there should be adequate clinical testing of all new food additives in advance of their sale to the public. And clinical testing means including all of the populations that are likely to use the product. If we are going to sell aspartame and things like it to kids, we should do clinical testing on kids and on pregnant women and on lactating women, or else we should not sell the product to them. And this should be done before the product is put on the market.

The testing, by the way, should be for more than one day. Several of the seizure and headache studies that industry has supported—including one, I gather, that is about to be published—involve giving a few doses, two or three doses, for one or two days. That is not what we see happens. We see symptoms, or we see complaints of symptoms, after people have taken the aspartame for weeks.

And so one-day and two-day studies as far as I am concerned are of no value.

Third, I think we need post-marketing surveillance. We need to have mandatory reporting of side effects or possible side effects, not voluntary reporting. I understand that the aspartame companies are in fact providing this information, and this is praiseworthy. It is just that society cannot, I think, depend on that all the time.

Fourth, I think there should be quantity labelling. I think, for instance, if an obstetrician tells a woman you can have up to half a gram of aspartame per day, there ought to be some mechanism by which she can find out how much she is consuming. I cannot understand why quantity labelling has not started.

And fifth, I think that there should be a panel appointed to advise the Food and Drug Administration, perhaps the Bureau of Foods, or perhaps better, it would seem, the combination of foods and drugs, to advise them on standardized tests for possible effects of food additives on brain and behavior.

When the Commissioner talked this morning about a no-effect dose, he meant the effects he was looking at; he did not mean the effects he was not looking at. And there is no process now within the Food and Drug Administration for even looking at possible effects of new food additives on brain and behavior.

I hope very much that some of these suggestions may find their way into revised mechanisms for dealing with the flood of new food additives that I think we will be seeing in the next few years.

Thank you.

[The prepared statement of Dr. Wurtman follows:]

STATEMENT BY DR. RICHARD J. WURTMAN
DIRECTOR, CLINICAL RESEARCH CENTER
MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Vast numbers of people in America and elsewhere now consume aspartame regularly, many sometimes eating or drinking amounts that are well in excess of the quantities that the Food and Drug Administration assumed people would consume when it authorized aspartame's inclusion in diet beverages and other foods. Thousands of people are sufficiently convinced that they personally suffered side-effects caused by aspartame to have written letters to the FDA about their experiences, and it can be assumed that very many more people--concerned about such side effects--have simply chosen to avoid the artificial sweetener (a choice not always possible in a society that consumes half or more of its meals outside the home). Within the scientific community real controversy persists concerning the safety of unlimited aspartame consumption for all people, and speakers at an international conference on aspartame (held in Washington in May, 1987) identified numerous sub-populations in which unlimited aspartame consumption could cause special risks (e.g., pregnant or lactating women; young children; people with a seizure history; people taking various medications).

One group of scientists, myself included, responds with anxiety to the ease with which relatively low aspartame doses can be shown to affect brain composition and function in experimental animals (and worry about the implications of such responses for the human brain); other scientists conclude that because aspartame has not been proved to be unsafe (in large-scale double-blind studies), it remains appropriate to allow everyone (except for homozygous phenylketonurics) to use as much of it as they like--and unnecessary even to indicate on food labels the amounts of the sweetener contained therein.

How can it be that we still know so little about the health effects of aspartame? And the next time a new food additive is introduced to the food supply, will aspartame's history repeat itself? (That is, years after its acceptance, will major doubts persist about the universal safety of the new additive?)

I believe that many of the problems that Society has faced in assessing the safety of aspartame could have been obviated had the use of this and other new food additives been regulated in a manner closer to the ways we regulate new drugs, particularly the over-the-counter drugs. There is no *a priori* reason to decide that a brand-new chemical (like aspartame) which will be placed in the Nation's food supply--and consumed by vast numbers of people who anticipate, perhaps incorrectly, that it will affect *only* the gustatory and nutritional properties of their foods--should be subject to *less* testing than one intended to be used as a drug, by much smaller numbers of people (who take it precisely *because* they desire its physiological effects and who believe, based on adequate evidence, that these effects justify risking its possible side-effects). I would like specifically to propose the following:

1. That the Food and Drug Administration be required to form *standing advisory committees*, like those which advise it about over-the-counter drugs, to determine which food-related problems actually require solutions involving new food additives (e.g., improving appearance or taste; reducing caloric density), and that these committees establish mandatory criteria by which the FDA will judge the extent to which candidate food additives actually solve the problem, and the relative risks of their side-effects.
2. That no new food additive be approved for sale prior to the completion of *adequate clinical testing*, which will include both unselected populations and people who might be at special risk of

suffering side-effects from the additive. Such high-risk populations might include infants and children--if it is intended that such "consumers" ultimately purchase products containing the additives; pregnant or lactating women and old people; people taking drugs which might interact, chemically or physiologically, with the additive.

3. That mechanisms of *Post-Marketing Surveillance* be established for new food additives, requiring that companies periodically report to the FDA any new findings that come to its attention bearing on the safety of each additive, and that companies immediately transmit to the FDA reports of possible *adverse reactions* to the additive.

4. That any food containing any new food additive be required to indicate, on its *label*, the amount of the additive present per package and per serving, as well as that additive's RDA.

5. That an Advisory Committee be established to recommend to the FDA *standardized tests* that can be used to uncover possible effects of candidate food additives on the *nervous system and/or behavior*, and that such testing be required before the additive can be approved for sale.

CONFERENCE ON DIETARY PHENYLALANINE AND BRAIN FUNCTION
MAY 8-10, 1987
WASHINGTON, DC

Richard J. Wurtman, M.D.
Massachusetts Institute of Technology

Summary

This conference has considered three sets of issues -- scientific, medical, and regulatory -- relating to possible effects of aspartame and of pure phenylalanine on the brain. What follows is a personal assessment of the status of those issues.

Scientific Issues

Compelling evidence has been presented that the consumption of aspartame or phenylalanine raises the plasma phenylalanine concentration and the plasma phenylalanine ratio (PHE/LNAA) (Caballero; Filer), and thereby elevates brain phenylalanine levels (Fernstrom). Moreover, this rise in brain phenylalanine can suppress the synthesis and release of dopamine (During) and perhaps other monoamine neurotransmitters (Lou). Whether or not a decrease in monoaminergic neurotransmission actually occurs after aspartame or phenylalanine consumption depends on the species and dose being tested: In experimental rodents, relatively low doses of aspartame or phenylalanine (e.g., 200 mg/kg) cause greater increases in plasma and brain tyrosine than in phenylalanine (because the livers of such animals exhibit very high phenylalanine hydroxylase activity, and thus rapidly convert most of the ingested phenylalanine to tyrosine). Consequently, monoaminergic neurotransmission (e.g., brain norepinephrine release) can actually be enhanced. However, in rodents receiving high aspartame doses (e.g., 1,000 mg/kg or greater) and, probably, in humans receiving any dose, blood and brain phenylalanine levels rise by more than those of tyrosine (Maher), and the phenylalanine suppresses dopamine synthesis (by inhibiting the enzyme tyrosine hydroxylase and by competing with tyrosine for uptake into the neuron). This species difference in the metabolism of phenylalanine is critically important to keep in mind when assessing the relevance of particular animal studies in predicting human responses to aspartame or phenylalanine (Wurtman).

Administration of aspartame or phenylalanine has been found in some (Spiers; Elsas; Krause) but not all (Wolraich; Lieberman; Elsas) studies to affect cognitive and attentive behaviors or electroencephalographic patterns in apparently-normal people (i.e., true normals and asymptomatic PKU heterozygotes).

Aspartame or phenylalanine can also act as a "co-epileptogen" in rodents treated with seizurogenic compounds (Maher; Garattini; Kim) or by kindling (Tilson). It is ineffective in some other animal models for human seizures (Jobe; Garattini). Tyrosine tends to be an antidote to this "co-epileptogenic" effect, as well as to the inhibition by phenylalanine of brain monoamine synthesis in animals (During) and humans (Lou).

The biochemical mechanism of phenylalanine's neurotoxicity (i.e., in PKU) may involve the brain enzyme ATP-sulfurylase, which is important in the biosynthesis of sulfatides (Hommes). At present, no information whatsoever is available concerning the threshold concentrations of phenylalanine in plasma or brain at which the amino acid begins to have cytotoxic effects or cause neuronal loss.

Medical Issues

Abundant anecdotal reports (summarized by Tollefson) describe an apparent temporal association between aspartame consumption and neurologic signs and symptoms (Johns; Schomer); however, to date, no studies have been published describing well-controlled studies. One preliminary report described an association between aspartame and headache (Koehler); another failed to observe such a link between aspartame and seizures (Shaywitz). Hence it cannot presently be determined whether aspartame has been a causative factor in these neurologic syndromes. It seems critically important that such studies now be done.

Inasmuch as most of the anecdotal case reports that associate aspartame consumption with neurologic sequellae describe these sequellae as occurring only after prolonged use of the sweetener, clinical studies designed to examine aspartame's role should be chronic (i.e., of at least several weeks' duration). Moreover, they should provide the sweetener according to a "worst-case" but reasonable protocol, e.g., as though it were being consumed in a pitcher of cold beverage being drunk on a hot afternoon, either without food or with foods (carbohydrates) that potentiate phenylalanine's uptake into the brain.

Regulatory Issues

At present, companies marketing products containing aspartame or other food additives are not required to file reports with the FDA describing possible adverse reactions to their products. Nor, of course, do such companies (or the FDA) routinely encourage physicians to enquire about such adverse reactions (Hattan). It seems critically important that the law be changed to make such filing mandatory: As this meeting has demonstrated, once a sufficient number of reports have been received describing a particular set of responses (Tollefson), it then becomes possible to design and conduct controlled clinical studies to test the association between the additive and the reaction.

At present, laws regulating the use of new food additives do not require periodic safety updates (analogous to "Phase IV" data on new drugs) from manufacturers of these additives. Moreover, there seems to be no established mechanism for incorporating into such safety updates new information that suggests previously-unsuspected ways in which an additive might be unsafe (for example, the concept of co-epileptogenicity).

At present, manufacturers of products containing new food additives are not required to list on their labels the amounts of the additive that the food (or additive package) contains. Hence it is impossible for most consumers to choose the amount of an additive that they will consume. In other countries, such quantity labeling is routinely required (Eisenberg).

Pure phenylalanine - both the l- and the d- forms - is now routinely available in health-food stores, even though its efficacy in treating the conditions underlying its sale has still to be demonstrated, and its consumption has yet to be shown safe (Young). In Canada, steps have recently been implemented to remove phenylalanine from the shelves. The legal basis underlying the sale of phenylalanine in American health-food stores is uncertain (Yingling).

It is obvious and also not surprising that this conference -- the first ever, to our knowledge, on "Dietary Phenylalanine and Brain Function", has raised many more questions from all three realms than it has answered. But it seems clear that these questions are important, and that the scientific, medical, and regulatory issues that underlie them will be with us for a long time to come.

Senator **Metzenbaum**. Thank you very much, Dr. Wurtman. You have certainly been a stalwart in maintaining your position.

What is your position at MIT?

Dr. **Wurtman**. Well, there are several. I am a professor, and I have been a professor for 18 years, of neuroscience. It is a basic science lab. We work on brain chemicals.

But secondly, as a physician, I am the Director of the research hospital, the Clinical Research Center. We do studies there on Alzheimer's disease, depression, et cetera.

And thirdly, I am a professor in the medical school, the joint Harvard/MIT Medical School, and in fact will be lecturing next week to the medical students.

Senator **Metzenbaum**. We have heard from the AMA, the American Academy of Pediatrics, the FDA, et cetera, all saying NutraSweet is safe. Yet you were quoted in a recent article as saying, "I think the likelihood is very strong that NutraSweet does produce serious and potentially damaging brain effects in a number of people."

How do you respond to that?

Dr. **Wurtman**. I think that science and the data on which we draw conclusions change. I think my concerns are real, but they should not be the basis for committees making policy statements.

I think what I would like to see happen is not a banning of NutraSweet but rather, research, good clinical investigation and more basic science research done on the compound itself, using susceptible groups, using dosage schedules that are meaningful. But also I think we should learn from our mistakes so that the next time an additive comes around, we can deal with it properly.

Senator **Metzenbaum**. How many clinical studies have been made of NutraSweet, to your knowledge?

Dr. **Wurtman**. Real, bona fide studies?

Senator **Metzenbaum**. Yes, clinical studies.

Dr. **Wurtman**. On possible effects, let us say, on brain diseases?

Senator **Metzenbaum**. Yes.

Dr. **Wurtman**. I am not aware of any. I understand there is one that is about to be published in the New England Journal. There may be some that are under way right now.

Senator **Metzenbaum**. Isn't that part of the problem, that you can do studies in the lab, you can do studies on animals, but there have been no clinical studies that have been reported on to date?

Dr. **Wurtman**. Yes, sir, this is, but it does not really have to be that way. And when we come up with new over-the-counter drugs, for instance, or new prescription drugs, certainly, but take the OTC ones, there are committees that sit and that define what must be demonstrated before the over-the-counter drug can be put on the market and committees that require annual follow-ups on additional studies and data as those data become available. And I think that we can do the same thing with food additives.

Senator **Metzenbaum**. Dr. Wurtman, NutraSweet has used an ad, and I would like you to take a look at it and give me your evaluation of it.

[Videotape shown]

Dr. **Wurtman**. Well, I think it is deceptive. I think the average layperson looking at that advertisement would conclude that when he is eating the constituents of NutraSweet, they will affect his body in the same way as if he were eating them in natural foods. And we know that is not the case, and the reason that is not the case is because when you have phenylalanine in NutraSweet, it zips right into the brain, because you do not have other amino acids there to block its entry. Whereas when you eat what cows make, then phenylalanine levels in brain do not go up; in fact, they go down.

Senator **Metzenbaum**. NutraSweet has used another ad, over here. "Over half the food you eat today will contain what is in NutraSweet. It is nothing mysterious. NutraSweet brand sweetener is made from two building blocks of protein (amino acids, in more scientific lingo). They are just like those found in fruits, vegetables, grains, meats and dairy products, and your body treats them no more differently than if they came from a peach or a string bean or a glass of milk. Which is all the more remarkable considering that NutraSweet tastes just like sugar. That is sweetness you can enjoy and feel good about."

Now, my staff spoke with the National Advertising Division of the Better Business Bureau, who informed us that they received a complaint about the ad and concluded that it was misleading, implying the combination of elements of NutraSweet occur in nature.

> The National Advertising Division concluded that an overall impression that TV and print advertisements might lead a consumer to believe that the combination exists in nature.

Do you have any comment to make on that, Dr. Wurtman?

Dr. **Wurtman**. Again, I think it is a misleading advertisement. That combination does not exist in nature. NutraSweet is a synthetic compound. There is nothing a priori wrong with synthetic compounds, but I think we have an obligation to study them and establish their safety. And also, we should not try to imply that they have the same fate in the body as naturally occurring foods.

Senator **Metzenbaum**. Thank you very much, Dr. Wurtman.

Any questions, Senator Hatch?

Senator **Hatch**. Yes, let me ask a few questions.

Welcome back to the Committee, Dr. Wurtman. I remember you from the previous hearing.

Dr. **Wurtman**. Thank you.

Senator **Hatch**. Your research on aspartame has dealt with its breakdown product, phenylalanine, which is a component of aspartame, and possible seizures in rodents; is that correct?

Dr. **Wurtman**. Yes, sir. My own research has dealt with the chemical effects in the brain. I have a colleague at the Massachusetts College of Pharmacy who has done the studies on seizures and rodents, Dr. Tim Maer.

Senator **Hatch**. And you believe you have demonstrated that rats have seizures when using aspartame?

Dr. **Wurtman**. No, it is not quite that way. I do not think aspartame causes seizures. I think that in those animals, the chemical changes it produces lower their threshold to some other causative agent.

Senator **Hatch**. So it is a triggering aspect, a chemical reaction that triggers seizures.

Dr. **Wurtman**. Well, it does not really trigger; it lowers the threshold.

Senator **Hatch**. Okay, so that seizures can occur.

Dr. **Wurtman**. That is right.

Senator **Hatch**. Mr. Chairman.

Senator **Metzenbaum**. Go ahead.

Senator **Hatch**. Dr. Dews, which would be more applicable to the human condition, research using rodents or research using primates?

Dr. **Dews**. Oh, as a general proposition, the primates would be preferred as a final animal to study.

Senator **Hatch**. Have any primate studies been performed that demonstrate seizure activity at high-level intakes of aspartame?

Dr. **Dews**. Not to my knowledge.

Senator **Metzenbaum**. I want to point out to my colleague, I just discussed with Dr. Wurtman, that is one of the problems. There have been no clinical studies.

Senator **Hatch**. I think there are two studies in primates that have been done which demonstrate no effect on seizure threshold. Can we submit those for the record?

Senator **Metzenbaum**. That have been completed?

Senator **Hatch**. As I understand it, there have been two studies made. Am I wrong on that?

Dr. **Dews**. There have been clinical studies. Could I make a comment on clinical studies?

Senator **Hatch**. Yes, and then I will go back to Dr. Wurtman.

Dr. **Dews**. Clinical studies, when one is looking for an effect and trying to determine whether that effect occurs with a given agent, then a clinical study is a very good way of going.

If, on the other hand, you are looking for whether there is a potential effect in one in a million people after they have been taking something for two years, then a clinical study, the clinical route, is not a good way of obtaining that information.

Senator **Hatch**. All right.

Dr. Wurtman, do you agree that research results must be reproduceable before they can be fully accepted as valid?

Dr. **Wurtman**. Absolutely, sir. I think that one doesn't really believe anything until four or five laboratories have come along and confirmed it—even stuff from one's own laboratory.

I do feel also, though, that there are certain safeguards that investigators can utilize to diminish the likelihood of publishing things that cannot be reproduced. For example, in my laboratory, we have a rule of three—three different people have to independently do the investigations, apart from each other, three different days, et cetera, before anything leaves the laboratory.

May I come back, though, sir, to a question you raised before that was unanswered?

Senator **Hatch**. Sure.

Dr. **Wurtman**. There may be experimental situations in which aspartame does not potentiate seizures. But as long as there are any in which it does, I think that is enough.

Senator **Hatch**. Okay.

Let me just ask Dr. Fernstrom this. You stated in the Journal of Clinical Nutrition, quote, "The rodent study by Wurtman and

Maher in which aspartame altered the seizure threshold appears to be the experimental exception rather than the standard."

Now, would you please elaborate on the apparent lack of reproducibility with regard to this study?

Dr. **Fernstrom**. Right. These are studies in rodents, and as an investigator, I have looked through the literature on this. Dr. Maher has published a study giving a certain dose of aspartame to look for its potentiation of a drug-induced seizure in rodents. This was published as an abstract.

There is another abstract that is now out, showing that this result cannot be reproduced, and there are other models of experimental seizures in animals, where studies have been done with aspartame using doses up to far in excess of what Dr. Maher has used, finding no effect whatsoever.

So the reason I wrote that comment was it appears to me, looking at all the data that are available, that there is not a reproducible effect here.

Dr. **Wurtman**. Can I comment on that, Senator?

Senator **Hatch**. Yes, of course.

Dr. **Wurtman**. Dr. Maher is not here to defend himself, so I will try to do it for him. He has an article that is appearing, I think, next month in the leading peer review journal, Neuropharmacology, for publishing things of this sort. It details effects of aspartame in three different types of seizure models. And in all three of those models, he found potentiation.

Similar data were obtained by Dr. Silvio Garretini, the extremely well-known, justifiably well-known, Dean of Italian Neuropharmacology at the Mario Negri Institute.

My suspicion is that when 50 studies are done in 50 different labs, 10 will find some effects and 40 will not, depending on the personality of the investigator, the phase of the moon, et cetera. But I think the important thing is does anybody find any positive findings, because we only use these animal models to give us a hint as to what might be occurring in people.

Senator **Hatch**. Yes. Well, Dr. Wurtman, since scientists must deal in statistics, is it possible to prove that any substance is absolutely safe or risk-free?

Dr. **Wurtman**. No, sir, I do not think it is possible to do that. I think we have to make cost benefit analyses. And one of the things that has been missing from food additives until now is some notion of benefit, and benefit for particular populations.

Senator **Hatch**. Yes. Well, the best you can do is prove safety to a reasonable certainty; is that correct?

Dr. **Wurtman**. Yes, sir.

Senator **Hatch**. That is the best you can do.

You would agree, I take it, that scientists who have criticized NutraSweet have merely raised questions, not made statements of scientific fact?

Dr. **Wurtman**. Yes, sir, I do agree with that.

Senator **Hatch**. You would agree with that. Would you further agree that there is a vast difference between raising scientific questions and making scientific statements of fact?

Dr. **Wurtman**. Yes, sir.

Senator HATCH. Okay. Now, there have been assertions that NutraSweet is buying off the opposition, that it offers research funds to critics in order to silence their criticism. It simply wants to ensure that the best research is available, is their claim, so that no criticism is left unchecked.

Now, as far as I am concerned, I know of no researchers that can be bought off, and I feel most scientific researchers are highly credible and honest men and women. And you yourself have received grants, as you mentioned in your opening remarks, from G.D. Searle and the NutraSweet people, and yet you have been one of the most vocal opponents of aspartame.

Dr. WURTMAN. Yes, sir.

Senator HATCH. I know that you have also received funds from other industry groups as well with regard to studying this, is that correct——

Dr. WURTMAN. Yes, sir.

Senator HATCH [continuing]. I think, about $175,000 from ILSI; and then you received about $165,000 from G.D. Searle in a contract that went between 1984 and 1987.

Dr. WURTMAN. Yes, sir.

Senator HATCH. And you received another approximately $62,500 to study the effects of phenylalanine, tyrosine and AFM on release of monoamine neurotransmitters; and then another approximately $100,000 on studies of phenylalanine metabolism in humans; plus you received honoraria of $20,000 in 1984-1985, and then another $30,000 in 1984 and 1985.

Dr. WURTMAN. No, that is not right, sir. That is not right.

Senator HATCH. Well, from Interneuron, Inc., you received some honoraria.

Dr. WURTMAN. No, no, that is not right.

Senator HATCH. You did not? You did not ever receive any honoraria from them?

Dr. WURTMAN. No. I would like to see it, but I have not.

Senator HATCH. Okay. Then, I am mistaken on that.

Dr. WURTMAN. Yes, but the other numbers are correct.

Senator HATCH. The only reason I am bringing this out is because I think it would be unreasonable for someone to assume that your receipt of these research funds may have an effect on your opinions with regard to aspartame, and I personally do not believe there are any top scientists in this country who will allow their judgments to be influenced one way or the other.

Dr. WURTMAN. May I comment on that, sir?

Senator HATCH. Yes.

Dr. WURTMAN. Well, if anybody thought they were buying my approval with those funds, I guess it is a textbook case on how not to do it, isn't it?

But there are two things, I think, that would fly a red flag for me. Firstly, it is the nature of things that I am responsible for—and by the way, I get none of these funds for myself—but I am responsible for between $3 and $4 million per year in research funds, because there are about 70 people whose mouths are fed from these funds. I think in the context of that large a budget, it is not terribly dangerous for me to receive 5 percent, or even 7 or 8 percent, from a particular source——

Senator HATCH. Or even 100 percent.

Dr. WURTMAN. Well, I would worry a little bit, sir, if an investigator received 50 percent or more of his support from a single industry source, because while there is the possibility of conflict of interest, I think at the very least it would be incumbent upon the investigator to make it very clear as a preamble in presenting his information where the support came from.

Senator HATCH. Well, I think what I am getting to is this, that even though you have received hundreds of thousands of dollars, I am not implying that you have done anything improper or that you have skewed your findings.

Neither should, I think, anybody imply that others have done the same, and I do not think you would accuse anybody of doing that, would you, in the scientific field?

Dr. WURTMAN. No, sir. But again, there is one thing I would be concerned with, and this is a distinction I made. It is one thing to receive research funds to your laboratory through your institution—in my case, MIT—none of the money going to you and all of the money being accountable for to the institution.

Senator HATCH. Yes.

Dr. WURTMAN. It is something quite different being a private paid consultant. I quit being a consultant for the Searle Company two years ago, because I felt that their intentions and my perceptions of what was needed were incompatible.

I organized with some of these people a scientific meeting here in May on phenylalanine and aspartame, and one of the tickets of admission was people had to indicate whether they had any kind of a professional association as consultants or what-have-you with industry.

A lot of very distinguished scientists did not come to the meeting because they were hiding, I think, and really unwilling to provide information about consultancies.

Senator HATCH. So you are concerned that some of the scientists may be skewing their findings.

Dr. WURTMAN. Well, I think it is terribly important that people be completely open and provide all information about their sources of support.

Senator HATCH. Oh, I do, too.

Senator METZENBAUM. Wasn't there a threat at one time of a veto of some funding for one of your projects?

Dr. WURTMAN. Yes, that was a sorry day, and that was one of the things that led me to terminate my consulting relationship.

I found an experimental neurologist, also the head of a Neurology Unit at two of the Harvard hospitals, Dr. Donald Schoemmer, who wanted to do I thought a very good study to see whether aspartame did facilitate seizures in people. And we were visited by somebody from the Searle Company, who I note is not with us today, and presented to him our intention to do so—not asking him for support, but telling him, because we thought it was fair that he should know about it. And he said that the organization to which we submitted our request, ILSI, he would see to it that they vetoed the support.

I have a letter that I turned in yesterday from Dr. Schoemmer, again, affirming that.

I think there are other people on this panel, Senator, who will also tell you similar stories in which they were encouraged to make applications for support and then given what they thought was either a run-around or worse.

Senator **METZENBAUM**. So that there is a tie-in quite often between subvention and coming out with the proper kind of report?

Dr. **WURTMAN**. It would appear to be that way.

Senator **HATCH**. But you are not sure. You are saying that you are concerned.

Dr. **WURTMAN**. That is correct.

Senator **METZENBAUM**. He had a threat; he had a threat of a veto.

Senator **HATCH**. I see. Dr. Wurtman, is it true that you received at least $15,000 in research funds from the sugar industry?

Dr. **WURTMAN**. No. I received $7,500 in research funds from the Sugar Association about three and a half years ago before getting a grant from the NIH; and I am very grateful to them because without those funds, there would have been no support at all.

The other funds that I received from them—I think it was $8,000—was for this phenylalanine meeting, but I think the Nutra-Sweet Company gave us $25,000—Coca-Cola, Pepsi-Cola, Nutra-Sweet—everybody gave us support for that, yes.

Senator **HATCH**. You see, my point is that I think it would be unreasonable for anybody to accuse you of trying to hit NutraSweet or G.D. Searle or anybody else because you received $15,000—$7,500 plus $8,000—from the sugar industry or from people in the sugar industry, because let us face it, the sugar industry does have a vested interest in banning aspartame. I do not believe you are biased in favor of the sugar industry because of that.

Dr. **WURTMAN**. Well, again, the caveat that I would have is I do not think it is wise for an investigator to receive a majority of his funding from a single industrial source, and if he or she does do so, I think it is incumbent upon him to make it very widely known that that is the situation.

And secondly, I think it is especially important that investigators be fully open about their consultantships, because these are basically private contracts between the firms with which they work.

Senator **HATCH**. Yes. In this particular instance, I do not think anybody is trying to hide the fact that they have research grants or otherwise.

Now, Dr. Wurtman, aspartame is known to be an aid to dieters. You say you have no evidence that it helps, but there is some evidence that it may be helpful.

Dr. **WURTMAN**. No, sir. I think the study that was reported in Cambridge about a month and a half ago—it was interesting to look at the press release that came out about the study and then to look at the study itself. It was done at the Deaconess Hospital by Dr. Blackburn. The press release said that in women who used aspartame while they were dieting lost, I think, 16 pounds in 6 months, and those who did not lost 13 pounds; whereas with men, it was the opposite. With men, they seemed to lose less weight if they took aspartame than if they did not.

Anyhow, there were no statistically different differences. When the information was presented at a scientific meeting, the investigator got it right, and what he said at the scientific meeting was that at least aspartame did not interfere with the diet.

I think it may very well be useful, but we do not know the answer to that yet.

Senator HATCH. Okay. But I have a couple more questions.

You recently patented a use for tryptophan which would, "diminish appetite and facilitate weight loss." Is that true?

Dr. WURTMAN. Well, I think it was seven years ago that Dr. Fernstrom, who is sitting here, and I jointly patented—let me read you the title of the patent—"Composition and Method for Suppressing Appetite for Calories as Carbohydrates". And what that patent had to do with was a weight reduction method.

At present we have very few drugs we can give the relatively few seriously obese people who need some kind of medication, and we found that giving tryptophan with carbohydrates would have this effect, at least in animals.

I should point out, sir, that that was prior to the time that I testified in favor of aspartame at the Board of Inquiry.

Senator HATCH. I have no problem with that. I am not finding fault with you. On your patent application number 4687763, one of the intended uses of tryptophan was as an artificial sweetener; is that correct?

Dr. WURTMAN. No, sir. I think your staff got that wrong, and I tried to explain it to them yesterday.

Senator HATCH. I do not think so.

Dr. WURTMAN. No. What you are reading there, sir, is it is possible to mix the tryptophan with a sweetened solution. If you look at the list of sweeteners in the patent, you will see what they are—they are sugar, glucose, dextrose, and in fact you will even see starch listed there. The important point is not the sweetness. The important point is the glycemic index, the ability to elicit insulin secretion.

My laboratory does not work on sweeteners. We have no competence to study sweeteners. I have never published a paper on sweeteners. And I thought I explained that to your staff yesterday.

Senator HATCH. Well, the only reason I bring it up is because in the patent description, the detailed description of specific embodiments, it says that "Tryptophan can be administered as free amino acids, esters, salts, neutral or synthetic polymers, or as constituents of food. The route of administration will generally be oral, for example, as a tablet sustained release capsule, drink, beverage sweetener, wafer candy, chewing gum, may be mixed with a mild stimulant such as caffeine for daytime use to override the sedative effect of tryptophan seen in some people, or used without a mild stimulant." That is the only reason that I thought maybe that was the case.

Dr. WURTMAN. Yes, well, it is not, sir.

Senator HATCH. Well, there is some indication, and some feel, that your patented use for tryptophan, if commercialized, could be construed as a competitor to aspartame. Whether that is true or not, I do not know. But can you——

Senator METZENBAUM. Wouldn't tryptophan be a drug described by a doctor, and not over-the-counter?

Dr. WURTMAN. Yes, sir. Of course it would be, yes.

Senator **Hatch**. I understand that.

Dr. **Wurtman**. I mean, if people are seriously suggesting that somebody interested in developing a drug to treat obesity would be against an artificial sweetener because they would be competing——

Senator **Hatch**. Well, let me say this. As I understand it, it would be a competitor for aspartame for people who want to control weight, and sales could be expected to go up if aspartame were banned. That is the argument that can be made.

Dr. **Wurtman**. Sir, I am sorry. I think there is no intellectual credence to that argument. I think there is no possibility that an anti-obesity drug would sell more if aspartame were taken off the market.

Senator **Hatch**. Let me just end with one question to Dr. Fernstrom. How did you get involved, and what is your comment with regard to what Dr. Wurtman has said?

Dr. **Fernstrom**. Well, I think the idea behind the original patent was—I was sort of thrown on this at the last minute, so I am guessing now, because I have not actually seen the real patent——

Dr. **Wurtman**. You do accept the royalties, don't you, John? You do accept the royalties, don't you?

Dr. **Fernstrom** [continuing]. I will answer that question in a minute, Dick——

Dr. **Wurtman**. Yes, okay.

Senator **Hatch**. Let him answer.

Dr. **Fernstrom** [continuing]. That it is a mixture of tryptophan and carbohydrate, with the idea that it would be an appetite suppressant. And the notion was that tryptophan by itself should be able to suppress appetite, and that when you mix in the carbohydrate, it does something to insulin secretion and amino acids in blood to further potentiate tryptophan's effects.

I was sort of thrown on that as the last minute as kind of a sop to me about ten years ago, and I frankly forgot about it, and I had already left my faculty position at MIT to go to the University of Pittsburgh when apparently, I guess, Dick succeeded in selling that license to some unsuspecting company.

I always thought the patent belonged to MIT, because they called me up one day and asked me did I have any violent objections to this; they had heard that I had. And I said from a scientific point of view, I have no problems with carbohydrate and tryptophan causing effects in the brain. Whether or not it has an appetite suppressant effect, let the buyer beware. But from a neurochemical point of view, I had no problems.

MIT sent me $1,000 as a royalty fee, and what has become of the thing since, I haven't a clue. I never followed it, and that is the only interaction I had with that patent.

Senator **Hatch**. I see.

Dr. **Wurtman**. If I could just point out, Senator, that it is necessary to sign a patent application and get it notarized. One does not add a name to a patent application. It is a legal document.

Dr. **Fernstrom**. I do not deny that I signed the application. But you know, MIT is the kind of place that is a very aggressive place, and it likes you to do things like this, and certainly my colleagues have trained me to some extent. But I certainly watch them do this. I had no direct participation in the formulation of this patent application, but I was asked if I wanted to be on it at the last minute, and I had no reason not to be, because from a biochemical point of view, the fact that was being stated was correct.

Senator HATCH. Well, thank you all.

Let me just say this. I think this points up that research scientists can differ—and there are plenty who differ with you, Dr. Wurtman, as you know, including the whole FDA. The only thing I worry about is why we are holding the hearing, because we knew all this during the last six years when we held four other hearings.

You have not said anything different today, from my recollection of past hearings nor have, you come up with any different conclusive findings. You raised the issue before, and we all acknowledge that there is no way of conclusively proving that any food or any additive has no risk to the population at-large. You acknowledge that yourself.

I think it is fair, and certainly wise, for us to do everything we can to make sure that additives are safe. Some question is, when does it end? I mean, when do you quit beating up the manufacturers of aspartame?

Senator METZENBAUM. I am going to have to move the hearing along.

Senator HATCH. Well, let me just finish.

Senator METZENBAUM. No; I only want to give the witnesses a chance to be heard—I like hearing you speak—it is beautiful.

Senator HATCH. I know you do, Howard.

Now, let me just say this to you. I am concerned because if there are new findings or there are new conclusions that can be reached by tough scientists, I think we ought to hold hearings on them. But we have gone into this forwards and backwards before, and I came here hoping I would hear some new information. Now, there may be, but I have not heard it. I am sure there will be——

Dr. WURTMAN. I am sure there will be. The reason I have not given new findings is that I knew that Drs. Elsas and Pardridge would.

Senator HATCH. All right. I will read the statements. But let me just say this to you—I hope it is something new.

Senator METZENBAUM. But you are not going to be here.

Senator HATCH. But I will read and I will pay very strict and close attention to the testimony.

I think there may be serious discrepancies regarding the dispute between Mr. Turner's position and the FDA in the record, Mr. Chairman, so I would also like to clear that up. I am concerned with some of the things Mr. Turner said, because I am not sure they were as accurate as they should be. Be that as it may, let us clear them up and make sure that this record is complete.

And I will be very interested, Dr. Elsas, in what you have to say, as well as the rest of you.

So with that, I am sorry that I took a little longer than I intended to take.

Senator METZENBAUM. So am I.

I will say that Mr. Turner has been a long-time advocate, and his statements have been well-respected over a period of many years, and he has been a prod in this area.

And it is important, Dr. Wurtman, before we leave you, that diabetics—I think we all agree that diabetics need sugar substitutes, and that we are not saying that sugar substitutes are not important for diabetics. I do not want anybody in range of my voice in connection with this hearing to think that we think that sugar substitutes are not critically important for people who are diabetics. I am sure you would agree.

Dr. **WURTMAN**. Oh, I absolutely agree, sir. I think that that is one of the groups for whom the substitutes are most important. I think we need some good clinical tests to establish the efficacy, but I am sure it will be there.

Senator **METZENBAUM**. Thank you very much.

Dr. Elsas?

Dr. **ELSAS**. Thank you, Senator Metzenbaum, particularly for inviting me to this hearing.

I feel like a babe in the woods. I have no previous contact with this type of hearing. But that is probably appropriate because I am a pediatrician, a Professor of Pediatrics at Emory, and have spent 25 years in the biomedical sciences, trying to prevent mental retardation and birth defects caused by excess phenylalanine. And therein lies my basic concern, that aspartame is in fact a well-known neurotoxin and teratogen which, in some as yet undefined dose, will both reversibly in the adult and irreversibly in the developing child or fetal brain, produce adverse effects. Aspartame is increasing in our world food supply without, I feel, appropriate prior investigation of its adverse effects on human brain function or appropriate surveillance at the present time.

Let me clarify these unanswered questions. One of those is "does phenylalanine excess occur with aspartame ingestion?" If so, "will it adversely affect human brain function?"

Now, those two basic questions, I was pleased to see, are being addressed about three years after a formal proposal was given to ILSI, through experiments defined this morning by Dr. Young. But they have not as yet been answered, and they therefore create considerable concern on how our population is being affected by aspartame.

Over the past two years, on my own and without funds from Federal sources, I have asked some questions about what kinds of brain function tests we can use and what dose or increase in blood phenylalanine affects those brain function tests.

Ingesting 34 milligrams of aspartame per kilogram per day chronically, which is well below the now 50 milligram per kilogram dose that is approved by the FDA, there is a two- to five-fold increase in blood phenylalanine. There is not a concomitant increase in other blood amino acids, so that we have disturbed the balance of our body's amino acid concentration in favor of a specific increase in phenylalanine.

Now let me give you a couple or three situations that are rather worrisome.

First of all, in the developing fetus—a situation not considered previously—the mother is supplying that fetus with nutrients. And if she were dieting, let's say, and increasing her blood phenylalanine uniquely by taking Crystal Lite or Kool Aid, or any of the various diet foods now, to maintain her weight, and increased her blood phenylalanine from its normal 50 to 150 *u*molesle by chronic ingestion at 34 milligrams of aspartame per kilo per day—which everyone agrees could be reached—the placenta will concentrate her blood phenylalanine two-fold. So the fetal blood circulation to her baby in utero, is now 300 μmole per liter of phenylalanine. The fetal brain then, as Dr. Pardridge will tell you, will increase further that concentration into the brain cells of that baby two- to four-fold. Those are neurotoxic levels in tissue culture and in many other circumstances.

This situation has not been studied in man. We have no research efforts in place to actively survey a cohort group, to find out whether chronic aspartame ingestion is adversely affecting our newborn population, either by producing microencephaly, mental retardation, or other birth defects that are associated with rises in blood phenylalanine. So that is one very worrisome area.

Number two. In children——

Senator METZENBAUM. Give us the first one in one sentence.

Dr. ELSAS. The first one. Their could be adverse effects of phenylalanine ingested by the pregnant mother-to-be on her growing fetus.

Senator METZENBAUM. Are deleterious?

Dr. ELSAS. Potentially deleterious—there is no answer. I have got to hurry now; I see my yellow light is on.

I will just skip over the next area, which is the concern that in the rapidly growing brain of the child from zero to six months, of age, when the velocity of brain growth is at its maximum; myelin sheaths are forming and the synapses are coming together. If the imbalance of increased blood phenylalanine were magnified in the brain cells, it could very easily disturb and produce irreversible damage to those insulations and synaptic formations in the brain of the developing child.

Finally, the third area is in the older child and adult. This is the area that I have specifically addressed, "what is the dose of phenylalanine charge at which cognition, neurotransmitter production—and brain electrical activity will be altered?" I hope these parameters will be part of the FAA study—particularly the mean power frequency of the EEG which is a very sensitive parameter. We have found changes in the EEG with physiologic changes in blood phenylalanine—that is, 10 to 50 micromolar changes specifically can slow that particular parameter.

So we have developed some more sensitive parameters of brain function which could now be addressed in more appropriate studies on effects of aspartame on the human brain.

I have some suggestions, but——

Senator METZENBAUM. Go ahead.

Dr. ELSAS. I think there should be immediate quantitative labelling of all aspartame-containing foods so that the consumer will have some idea of how much phenylalanine he or she is ingesting. I think there should be an immediate moratorium on the addition of aspartame to more foods and particularly remove it from low-protein beverages, where it is being ingested as a specific amino acid and from foods and medications to which children are exposed. And I am particularly angry at the type of advertising that we have seen here today that is promoting the sale of a neurotoxin in the childhood age group.

And finally, I think funds must be made available, not controlled by industry, for further research, using these newer technologies and approaches to parameters of human brain function. We should evaluate in a cohort-control study the effects of aspartame on the population of newborns. We currently have no active surveillance at all—and, I notice, no complaints, because nobody knows they are supposed to complain. I also think there should be active research funded in some way outside of industry to determine the dose relationships of phenylalanine effects on brain function.

[The prepared statement of Dr. Elsas follows:]

STATEMENT BY DR. LOUIS J. ELSAS, II, M.D.
DIRECTOR, DIVISION OF MEDICAL GENETICS
PROFESSOR OF PEDIATRICS

COMMITTEE OF LABOR AND HUMAN RESOURCES

"NUTRASWEET: HEALTH AND SAFETY CONCERNS"

NOVEMBER 3, 1987

EMORY UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF PEDIATRICS
2040 Ridgewood Drive, N.E. Atlanta, Georgia 30322

DIVISION OF
MEDICAL GENETICS

(404) 727-5840

Statement for the Labor and Human Resources Committee, U.S. Senate

I have considerable concern for the increased dissemination and consumption of the sweetener, aspartame (1-methyl N-L-α-aspartyl-L-phenylalanine) in our world food supply. This artificial dipeptide is hydrolyzed by the intestinal tract to produce L-phenylalanine which in excess is a known neurotoxin. Normal humans do not metabolize phenylalanine as efficiently as do lower species such as rodents and thus most of the previous studies in Aspartame effects on rats are irrelevant to the question, "does phenylalanine excess occur with Aspartame ingestion?" and if so "will it adversely affect human brain function?"

Preliminary studies in my laboratory provide tentative positive answers to both questions. Many studies of both acute and chronic ingestion of 34 mg Aspartame/kg/day have demonstrated a two to five fold increase in semi-fasting blood phenylalanine concentrations (from approximately 50 to 250 μM) without concomitant increases in tyrosine or other aminoacids. The degree of increase by normal humans depends on several variables including the efficiency of gut transport, liver utilization, and growth rates. It was thought by many scientists and clinicians that this degree of blood phenylalanine increase would not affect brain function. However, currently available information indicates that this is not true.

1) In the developing fetus such a rise in maternal blood phenylalanine could be magnified four to six fold by the concentrative efforts of the placenta and fetal blood brain barrier. Thus a maternal phenylalanine of 150 μM could reach 900 μM in the developing fetal brain cell and this concentration kills such cells in tissue culture. The effect of such an increased fetal brain concentrations *in vivo* would probably be much more subtle and expressed as mental retardation, microcephaly, or potential certain birth defects.

2) In the rapidly growing post-natal brain (children of 0-12 months) irreversible brain damage could occur by the same mechanism.

3) In the adult we have found that changes in blood phenylalanine in these concentration ranges are associated with slowing of the electroencephalogram, and prolongation of cognitive function tests. Fortunately, these effects on the mature brain are reversible but provide clear evidence for a negative effect on sensitive parameters of brain function.

In view of these new (and confirmation of old) research findings I suggest the following:

1) Immediate quantitative labeling of all aspartame-containing foods, so the consumer will know how much phenylalanine he/she is ingesting.

2) Declare an immediate moratorium on addition of aspartame to more foods and remove it from all low-protein beverages, foods, and children's medications.

3) Provide funds not controlled by industry to:

   a) Allow active surveillance for potential side-effects of aspartame on newborns whose mothers dieted with Nutrasweet^{R} (Aspartame)-containing foods.

   b) Allow active evaluation of other users whose complaints cannot be adequately studied at present.

   c) Clarify the dose relationship and mechanisms by which L-phenylalanine affects human brain function.

Respectfully submitted

Louis J Elsas II MD.

Louis J. Elsas, II, M.D.
Director, Division of Medical
Genetics
Professor of Pediatrics

Enclose: 3 reprints
Curriculum vitae

Senator METZENBAUM. Dr. Elsas, since Senator Hatch saw fit to go into the funding question, I will ask you, are your studies funded by industry?

Dr. ELSAS. No, sir. I had a research grant three years ago, for three years, from the March of Dimes, to study the effects of phenylalanine on human brain function. When the political issue got to aspartame, the society decided not to refund that. So all of the funding that is going on now—and the reason it is so slow has been through my own division's efforts, personal funds, and university-based funds.

Senator METZENBAUM. What do you think of our present system for funding scientific research?

Dr. ELSAS. I think the NIH is superb. I think there is a lot of concern about how industry and the FDA interact, where industry is made responsible for developing the data to support its own contentions. There is not a broad enough scientific base, such as an RFA, as we call it at NIH—research funds available—requesting input from the whole scientific community, stating that funds are available to investigate a certain area. In that way, you would get in an unbiased approach—what the questions are which we need to ask? That is the problem here today. The questions about phenylalamine effects on human brain function have not been asked. So we have spent millions of dollars through our current system on mostly irrevelant experiments without approaching those particular questions.

Senator METZENBAUM. What about the advertising campaign that NutraSweet puts on, and are you concerned about that?

Dr. ELSAS. Yes, sir.

Senator METZENBAUM. In what way?

Dr. ELSAS. I am mostly concerned that it gives the false impression that NutraSweet is good for you, that it is nature's best, and that it might even be good for children to take. A lot of the ads recently have shown children with the little ying and yang NutraSweet thing on it, making it sound like you should go with your mommy to the grocery store and look for that, and be sure that you buy that because it is real sweet and good.

Senator METZENBAUM. Can you tell the Committee about your own experiences with the International Life Sciences Institute?

Dr. ELSAS. Yes, sir. It was not good.

Senator METZENBAUM. Who is that group, can you tell us?

Dr. ELSAS. Well, Dr. Dews is right here; he can probably give you more personal information about it, because I have never gotten any feedback from them. But I was asked after issuing concerns both privately and then publicly on "Nightline" to give them a specific protocol for how I would approach these concerns. I did this. I wrote it up completely in a research grant format; submitted it through ILSI for their review, and basically, got a few phone calls from Dr. Dews over a prolonged period of time, stating that they had problems, but without ever a written peer review of criticism.

So I basically never got funded; that is the bottom line. And the ideas are now reappearing three years later in other places funded by industry.

Senator METZENBAUM. ILSI is pretty much the coordinating group for funding in the food and beverage industry, including pops, carbonated drinks, NutraSweet itself; is that correct?

Dr. ELSAS. As far as I know, that is correct, sir. I am not an expert on ILSI; I have repressed that experience.

Senator METZENBAUM. It is my understanding that Dr. Pardridge has to catch a plane, so I am going to pass on to him. But I appreciate your testimony, Dr. Elsas, and I am only sorry Senator Hatch was not here to hear you comment on the fact that—at least, the inference; it is not a fact—that if the information or the research is not going to be supportive of their position, that sometimes one does not get supported by organizations such as ILSI, NutraSweet and others.

Do you think that general conclusion of mine might be inappropriate, or appropriate?

Dr. ELSAS. Sir, I think that is very cogent and appropriate.

Senator METZENBAUM. Thank you very much.

Would you agree with that, Dr. Wurtman?

Dr. WURTMAN. Yes, sir.

Senator METZENBAUM. Thank you.

Dr. Pardridge, we are happy to hear from you, sir.

Dr. PARDRIDGE. Thank you, Senator, and thank you for having me.

I am a Professor of Medicine at the University of California, a practicing endocrinologist, and I have been doing neuroscience research on the blood-brain barrier transport of phenylalanine and other substances since 1970.

I believe in the discussion this morning, there are three key scientific food policy questions that have really not been properly illuminated.

The first question is the dosage problem. We are led to believe by the FDA this morning that the typical consumer will have 2 to 4 milligrams per kilogram of aspartame per day; that the 99th percentile intake is 34 milligrams per kilograms per day; and that the advisable daily intake or ADI is 50 milligrams per kilogram per day.

Now, the layperson sitting in the audience is really is in no position to analyze these esoteric numbers. But if we put it in a different context and recognize that 50 milligrams per kilogram per day is equal to 5 servings of NutraSweet per 50-pound body weight, we can see that children, owing to their reduced body weight, are at great risk for overconsumption of NutraSweet.

All one has to do in this room is look up at that chart and ask yourself if a 50-pound or 60-pound 7 year-old is going to consume 5 or 6 servings of that per day. If they are, then they have consumed 50 milligrams per kilogram per day, or the advisable daily intake.

Now, an 11-year study in the literature has already shown this, that the average 7-to-12-year-old, when made freely available to products like that, consumes 5 servings per 50-pound body weight per day, and up to 77 milligrams per kilogram per day.

Senator METZENBAUM. That is the average?

Dr. PARDRIDGE. The average in children is the ADI—5 servings per 50-pound body weight. Ask yourself: Would an average child have 5 servings? I think the answer is yes.

Another study by Porikos in obese subjects showed that the average intake was 20 milligrams per kilogram per day, or 2 servings per 50-pound body weight, and that obese adults consume up to 36 milligrams per kilogram per day, even in the face of that high body weight.

Now, if you accept the premise of the first question, that some individuals and in fact many children consume near the advisable daily intake of 50 milligrams per kilogram per day, then you must ask yourself what level of increase in blood phenylalanine will be concomitant with that ingestion of NutraSweet. And the answer is that your blood phenylalanine will rise three- to four-fold. That is not 10 percent or 20 percent. That is 300 to 400 percent. And this study has been done by Drs. Stegink and Filer, which was funded by the industry.

If you now accept that many individuals, particularly children, consume 50 milligrams per kilogram per day, or 5 servings per 50-pound body weight per day, and that they enjoy a four-fold increase in their blood phenylalanine, the third question that must now be addressed is, are there any untoward effects on the human brain that are associated with a four-fold increase in phenylalanine, bearing in mind that this molecule is a known neurotoxin?

And three studies come to mind. One study shows that when blood phenylalanine in pregnant mothers is increased five-fold, there is a 10-point drop in the I.Q. of the baby born of that mother.

Senator **Metzenbaum**. A 10-point drop in what?

Dr. **Pardridge**. In the baby born of that mother; a 10-point drop in I.Q. of the baby born of that mother.

Senator **Metzenbaum**. Of I.Q. All right.

Dr. **Pardridge**. A second study shows that if you measure choice reaction time, a test of higher cognitive function in humans, that when their blood phenylalanine is increased six-fold, there is a 10 percent shift in your ability to make a key decision before a video screen.

And a more recent study by Dr. Elsas has shown that there are quantitative changes in the human electroencephalogram when the blood phenylalanine is raised three-fold—something that clearly will happen in children who consume near 5 servings per 50-pound body weight.

So if I may summarize, phenylalanine is a known neurotoxin, and the food industry added nearly 8,000 tons of aspartame to the food supply in 1986, which amounts to approximately 8 million pounds of phenylalanine added to our food supply in a single year.

The consumption of aspartame has increased exponentially since its introduction in 1981. The 1986 consumption of aspartame in the United States was equal to nearly 22 percent of the 1986 consumption of refined sugar when one allows for a 200-fold increase in sweetener potency of aspartame relative to sugar.

With the enormous selective infusion of phenylalanine into the food supply, the key questions before the United States Congress and other scientific and medical organizations are whether selective increases in the blood phenylalanine level on the order of 200 micromolar or four-fold above normal, are to be expected with liberal intake of aspartame, and whether blood phenylalanine increases of this magnitude have untoward effects on the human brain.

Thank you.

[The prepared statement of Dr. Pardridge follows:]

UNIVERSITY OF CALIFORNIA, LOS ANGELES

WILLIAM M. PARDRIDGE, M.D.
Professor of Medicine

Department of Medicine
Division of Endocrinology
and
Brain Research Institute
Blood-Brain Barrier Laboratory

UCLA School of Medicine
Los Angeles, California
90024 (U.S.A.)
Tel. (213) 825-8858
or (213) 206-8305
Telex 9103427597

November 3, 1987

Statement of William M. Pardridge, M.D. Before
the United States Senate Committee
on Labor and Human Resources:

I have concerns regarding the widespread utilization of aspartame as a common nonnutritive sweetener (1, 2). Aspartame is a protein-like substance that is composed of two amino acids (aspartic acid and phenylalanine) and methanol. I believe the aspartic acid and methanol portions of aspartame are harmless. However, aspartame usage in high doses can lead to significant increases in blood phenylalanine. It is this increase in blood phenylalanine following aspartame consumption that is of concern to me. The basis for my concerns are three-fold.

1. Although industry estimates of individual aspartame intake are approximately 10 mg/kg per day, and the FDAs advisable daily intake (ADI) is 50 mg/kg per day, I believe that a significant portion of the population, particularly children, will consume upwards of 50 mg/kg per day, or approximately the ADI. In layman's terms, a dose of 50 mg/kg per day is approximately 5 servings per 50 lb body weight per day. While it is true that most 150 lb adults will not come close to consuming 15 servings per day, I believe that children, owing to their reduced body weight, will consume up to five servings per 50 lb body weight per day and approximate, or exceed, the ADI. Indeed 11 year-old studies have shown that when 7-12 year-old children have free access to a liberal supply of aspartame-sweetened products in their diet, their average consumption is 50 mg/kg per day and ranges up to 77 mg/kg per day (3). Since aspartame can be found in soft drinks, fruit juices, breakfast cereals, gelatin, puddings, milk shakes, and a whole host of other products, it is not surprising that a typical 7-12 year-old child may consume up to five servings per 50 lb body weight per day. The industry notion that children consume much less than 10 mg/kg per day must be categorically rejected, when it is recognized that the consumption of a single 12-oz can of cola by a 50 lb 7-year-old is already a dosage of 10 mg/kg per day.

2. If it is granted that many children and some adults will consume up to 50 mg/kg per day of aspartame (i.e., about five servings per 50 lb body weight per day) then it should also be recognized that data in the medical literature indicate that this dosage of aspartame will result in a doubling of blood phenylalanine in normal individuals and at least a tripling of blood phenylalanine in subjects who are heterozygous for the phenylketonuric (PKU) trait (4). The estimate of individuals with PKU heterozygocity (i.e., the condition associated with slow metabolism of dietary phenyalalanine) is believed to range anywhere from 4-20 million individuals in the United States (5). Since the normal blood phenylalanine concentration is approximately 50 µM, the blood phenylalanine level will rise to 100-150 µM in individuals who consume approximately 50 mg/kg per day of aspartame (4).

3. My third concern is that there are data in the medical literature which indicate that a tripling of blood phenylalanine to the level of approximately 150-200 µM concentrations may have untoward effects on the human brain. One study suggests that mothers who have a blood phenylalanine concentration of 250 µM bear offspring with a 10 point drop in IQ (5). Another study indicates that when blood phenylalanine is increased to the 250 µM concentration, there is a 10% change in choice reaction time, a test of higher cognitive function in humans (6). More recently, another study has shown that when blood phenylalanine is increased into the range of approximately 150-200 µM, there are quantitative changes in the electroencephalogram in humans (7).

Phenylalanine is a known neurotoxin, and the food industry added nearly 8,000 tons of aspartame to the food supply in 1986, which amounts to approximately 8 million lb of phenylalanine. The consumption of aspartame has increased exponentially since its introduction in 1981. The 1986 consumption of aspartame in the United States was equal to nearly 22% of the 1986 consumption of refined sugar (allowing for a 200-fold increase in sweetener potency of aspartame relative to sugar). With this enormous selective infusion of phenylalanine into the food supply, the key questions before the United States Congress and other scientific and medical organizations are whether selective increases in the blood phenylalanine level on the order of 200 µM are to be expected with liberal intake of aspartame, and whether blood phenylalanine increases of this magnitude have untoward effects on the human brain.

Yours very truly,

W. Pardridge

William M. Pardridge, M.D.
Professor of Medicine

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Senator METZENBAUM. Dr. Pardridge, let me just learn a little bit about yourself. You are a Professor of Medicine at the University of California?

Dr. PARDRIDGE. Yes, sir.

Senator METZENBAUM. Can you tell us some more about yourself? You are in the Division of Endocrinology and Brain Research Institute.

Dr. PARDRIDGE. I am a member of the Brain Research Institute. I am the director of the Blood-Brain Barrier Laboratory. The blood-brain barrier is more or less the gatekeeper of the brain, that allows phenylalanine and other amino acids into the brain. I am a practicing internist and endocrinologist. I perform clinical rounds in the UCLA Medical Center. And I run a very active laboratory that consists of 15 individuals, all working on various aspects of blood-brain barrier.

Senator METZENBAUM. And did ILSI once fund a study for you?

Dr. PARDRIDGE. ILSI in 1985 funded a study which showed that the human blood-brain barrier is nearly identical to the rat blood-brain barrier in terms of sensitivity to amino acid blockade by increased blood phenylalanine. That allowed extrapolation of Dr. Wurtman's studies in rats to the human condition.

Senator METZENBAUM. And have you had any other private funding?

Dr. PARDRIDGE. From ILSI?

Senator METZENBAUM. ILSI or any other group.

Dr. PARDRIDGE. No. I submitted two other grants to ILSI, but they were turned down. But I do not see how these funding issues are the important questions. The important questions are the dosage problem that I have raised. We have to get away from this 2 to 4 milligrams per kilogram idea that the FDA has been foisting on people and recognize that children will have about 5 or 6 servings of that stuff per day, and that they are going to get up into the ADI, and that the blood level of phenylalanine is going to rise, and that is going to have untoward effects on the human brain.

Senator METZENBAUM. Your point is that accepting the FDA's own figures as to where it is dangerous, that that is a reality of life today for the average consumer of aspartame, and that therefore there is an at-risk problem; am I understanding you correctly?

Dr. PARDRIDGE. Not only the consumer, but medical organizations. The American Diabetes Association is led to believe that a typical 7 year-old diabetic child on insulin, avoiding sugar, will consume considerably less—10-fold less—than the advisable daily intake. I ask if that 7 year-old diabetic child, who weighs 50 to 60 pounds, is he going to have 5 or 6 of those products, one each of those products. If he is, then the ADA and the FDA are wrong. The consumption of this substance can be considerably high, particularly in children.

Senator METZENBAUM. What do you think we ought to do?

Dr. PARDRIDGE. I think there should be quantitative labelling of all products immediately, so that physicians when confronted with a possible aspartame-related problem, can compute through a careful nutritional history the amount of milligrams per kilogram per day ingested. If it is 5 to 10 milligrams per kilogram, then I would not attribute that symptom complex to aspartame ingestion. If it is

40, 50, 60 milligrams per day or above, then I would seriously investigate the role of aspartame in their clinical problem.

Senator **METZENBAUM**. Dr. Elsas, I gather you would agree also that labelling would be a major asset in coping with this problem while clinical research is provided for?

Dr. **ELSAS**. Yes, sir, I do.

Senator **METZENBAUM**. And Dr. Wurtman?

Dr. **WURTMAN**. Yes, sir, I do.

Senator **METZENBAUM**. Thank you very much.

Dr. Dews, we are happy to have you with us.

Dr. **DEWS**. Senator Metzenbaum, thank you very much for the opportunity to appear before you today.

My name is Peter Dews. I am Professor of Psychiatry and Psychobiology at Harvard Medical School and have been for many years. During that time, I have been asked to give advice to a wide variety of organizations, including governmental organizations, National Institute on Drug Abuse, National Aeronautics and Space Administration; I have served on the National Advisory Councils of both of these, as well as on technical review committees of the U.S. Army, the U.S. Air Force, the Consumer Product Safety Agency, the Environmental Protection Agency, the National Institute of Environmental Health Sciences. I am currently advising the National Institute of Mental Health on its Advisory Council and several task forces. I have been a consultant to a number of industrial organizations, individual and collectively. And I have never put that list together before, but having done it, I realize why my wife asks, "Why are you running around so much?"

It is a privilege to be asked to comment on aspartame today. I have spent the greater part of my life studying pharmacology and behavioral effects of agents. The methods of study and the results obtained on aspartame are entirely familiar to me.

I have not personally received grants to study aspartame, nor have I published research on aspartame.

My involvement with aspartame began in 1983 when I was approached by the International Life Sciences Institute, ILSI, to serve as one of several consultants to advise on whether a program of scientific research on aspartame should be started by ILSI. That job involved becoming familiar with the work that had been done on aspartame, and since that time I have kept up-to-date on the significant literature and findings relative to aspartame in the diet.

And let me say right at the beginning that my bottom line is going to be almost identical with Dr. Wurtman's in that I think any agent that is taken by 100 million or so Americans most days should be the subject of continuing research investigations.

Senator **METZENBAUM**. Would you agree also that labelling of the amount of the product would be helpful?

Dr. **DEWS**. I have really given very little thought to the labelling issue, Senator. It would seem to me that the case for labelling the amounts of everything on everything is something that is very hard to dispute on principle. I cannot argue with the idea of giving people all the information. Its effect in terms of really informing people about what is important and what is not important, I cannot speak to, and it simply is possible that a surfeit of information would obscure the important parts of the information. But I am not giving you an opinion, sir. It is something that I have not given much thought to and have not come to a conclusion on.

Senator METZENBAUM. It would seem to me—wouldn't it to you, Doctor—that when people such as Dr. Pardridge and Dr. Elsas and Dr. Wurtman and others—and even the FDA—indicate that the amount of intake can have an impact upon the individual, that the only way the individual has to protect himself or herself is to know the facts; and that there is very little to be lost by labelling and a great deal possibly to be gained. Wouldn't you agree?

Dr. DEWS. I would not accept the proposition that there are a lot of people out there who are going to be adversely affected or not affected according to how much they take. I think the evidence is, as was presented by the Food and Drug Administration, that there may be a few people out there with idiosyncratic and allergic reactions to aspartame, but for the rest of the population, the only population that there is any evidence of risk is the people with diseases related to phenylketonuria, and they are in trouble with their whole diet, and aspartame is simply part of that.

But for the rest of the population, I would not accept that there is any evidence of any harmful effects.

I think early in the testimony, it was suggested that the Food and Drug Administration need conclusive evidence for harm before they can take any actions. I certainly do not think that is the case. I think that if they are given any substantive evidence, any evidence that has any credibility, that they can immediately initiate actions, call for additional studies, and make modifications to their licensing.

Senator METZENBAUM. The Food and Drug Commissioner today said, "Thus, the safety considerations of the compound would focus on the quantitative levels consumed, not the qualitative nature of the compound." It would seem to me that that would pretty much support the concept, the approach, of labelling as a very first step. And I am wondering whether or not you would not arrive at that same conclusion under those circumstances?

Dr. DEWS. Please do not think I am arguing against quantitative labelling. I simply have not formed an opinion. I do feel that a simplistic solution, as what harm can be done by telling the people this and telling the people that cannot possibly do any harm, is really not necessarily the case, and it is possible to confuse the issue by issuing too much information.

In this particular instance, I simply have not concerned myself with it.

Senator METZENBAUM. Dr. Dews, is it fair to say this particular subject is not especially your area of expertise?

Dr. DEWS. Well, it depends on how narrowly you define my area of expertise. I have been working with agents; I have been looking for behavioral effects of agents in a way that neither Dr. Elsas nor Dr. Pardridge have for 25 years. So from that point of view, I have as much expertise as anybody in the country.

From the point of view of specifically looking at aspartame, I have not studied aspartame; but neither has either Dr. Elsas or Dr. Pardridge, though they have studied phenylalanine. So it is a sort of trade-off.

Senator METZENBAUM. You have never done any research on the effects of amino acids on brain chemistry?

Dr. DEWS. I have never done any published—studies have been done in my lab. I have never done any published work.

Senator METZENBAUM. Nor on phenylalanine's effect on children and pregnant women?

Dr. DEWS. No, no, none.

Senator METZENBAUM. On seizure susceptibility?

Dr. DEWS. I have done work on seizure susceptibility, but not specifically with phenylalanine. But I have read the literature, and it is very close to things that I have done.

Senator METZENBAUM. And you are a professor of psychiatry.

Dr. DEWS. Psychiatry and psychobiology.

Senator METZENBAUM. And psychobiology. And what is your connection to the International Life Sciences Institute? I think that body is funded by NutraSweet and the soft drink industry, is it not?

Dr. DEWS. In very small part. I welcome the opportunity of setting the record straight. ILSI has come up a number of times this morning. My relation with it has been that I have been a consultant to the organization since its inception. It is now an organization with something like 12 to 14 technical committees. It is an international organization with branches in Europe, in Australia, in Japan. Something like 154 companies are members of ILSI, of which NutraSweet is just one. Most of the activities—there is a foundation associated with it; there is a Risk Science Institute that I have done a lot of work for—but much of the other work is done through a series of individual technical committees where the funds come from members of industry, both suppliers and consumers, and they pool their funds, acquire scientific advisers, and try to address research questions relative to the areas they are dealing with.

I have been associated with two committees, the Caffeine Committee and the Aspartame Committee. I am more interested in defending the integrity of the research activities than I am in defending the product itself.

I will testify that of the applications that have been received by the Aspartame Committee for review, together with two or three other expert consultants, we have considered all these applications, and I can testify to my direct knowledge that no issue other than science and some relevance to aspartame has been included in the criteria for funding or not funding. There has never been any instance where funds have been given for political reasons or funds have been withheld because somebody has said something that some members of the committee did not like.

And furthermore, no member of the committee has anything like a veto power over the actions of the committee. The decisions are made by consensus, usually unanimous, but not necessarily so; by the majority of the committee being willing to fund a particular piece of research. The advice of the scientific advisers has been exclusively on what was scientifically valid and good and of necessity some relevance to the subject.

Senator METZENBAUM. Thank you very much, Dr. Dews.

Dr. Fernstrom?

Dr. **Fernstrom**. May I make an opening statement, Senator?

Senator **Metzenbaum**. Surely.

Dr. **Fernstrom**. Thank you.

Thank you very much for inviting me to appear today.

My name is John Fernstrom, and I am Associate Professor of Psychiatry and Behavioral Neuroscience in the Department of Psychiatry at the University of Pittsburgh. I have been on the faculty since 1982, and prior to joining the University of Pittsburgh, I was a faculty member at MIT for a number of years in the then Department of Nutrition and Food Science.

My main area of research over the past 17 years has been on the effects of amino acids and the diet on brain neurotransmitter formation, an area that is relevant to today's discussion. I am a Ph.D., I should add.

For today, the topic of discussion is aspartame, and in particular the phenylalanine contained in it. Phenylalanine is an amino acid that reputedly can influence neurotransmitter formation in brain, and because of this someone with my research interests would be interested in exploring for such effects, in my case using rats.

Over the past five years, therefore, my lab has conducted a number of studies to determine whether aspartame ingestion can influence the formation of brain neurotransmitters in rats. But first we used what then were considered high doses of aspartame and found essentially no effects on transmitter formation. These results were published in 1983 in a peer reviewed journal.

We then conducted further studies using extremely large amounts of aspartame and found some transmitter changes. However, we also found that the amounts of aspartame needed to produce these changes were extremely high, beyond anything that a human could ever consume.

Senator **Metzenbaum**. Now, would you, Dr. Fernstrom, at that point comment on Dr. Pardridge's testimony on that same subject, which is 100 percent opposite yours. Is he totally alone?

Dr. **Fernstrom**. Well, I look at that chart up there, and I do not see intake levels, and I cannot interpret anything from that chart.

Senator **Metzenbaum**. That is not his chart.

Dr. **Fernstrom**. Well, I do not know whose chart it is. But my son is five years old, and he cannot consume one can of aspartame-containing soda pop. I cannot imagine him drinking five cans of aspartame-containing soda pop a day. And therefore, I cannot imagine a child taking that ADI. Fifty milligrams per kilogram is five cans of soda pop. And there is no way my 20-kilogram kid could do that.

Senator **Metzenbaum**. Well, he can have some Jello——

Dr. **Fernstrom**. They all have different amounts of aspartame in them, Senator.

Senator **Metzenbaum**. Yes, but we cannot tell the amount. Incidentally, we have gum; he could have Lifesavers; he could have Crystal Lite; he could have Metamucil; he could have Lipton Tea.

[Applause.]

Senator **Metzenbaum**. He could have a lot of things; he does not have to have just five cans of pop.

Dr. **Fernstrom**. Well, I would not give my kid Metamucil; I don't know about you. [Laughter.]

Dr. FERNSTROM. But the point is that Dr. Pardridge is trying to tell us that my child is going to consume 50 milligrams per kilogram, and the only way he can do that is by drinking five cans of that Diet Coke. And I maintain, having lived with him for five years now, there is no way he is going to do that. And I think if you start looking at the levels of intake, or the levels——

Senator METZENBAUM. Do you ever give your kid Swiss Miss Hot Cocoa Mix? That has NutraSweet. Or do you ever give him Carnation Instant Breakfast, No Sugar Added? That has got NutraSweet. Do you give him any of those?

Dr. FERNSTROM. Sure, I do.

Senator METZENBAUM. I mean, the problem, I think, Dr. Fernstrom, is that this product is found even in over-the-counter drugs. It is pervasive. Wherever you turn, you see the logo of NutraSweet. They have done a magnificent job of marketing. I just heard the other day they are now going to put it into baked goods, and I am told that at high heat levels there is a special impact upon the phenylalanine. And the concern is that you say no problem at all; these men all say we do not know what the problem is, but there is some kind of a problem out there, and we think we ought to find out more about it.

Dr. FERNSTROM. Well, I hear you saying two things. On the one hand, you are buying that there are biologic effects of this compound, which leads you to say how much aspartame is in those cans of things and to ask how much should we be given.

My research over the years as well as that of other basic investigators seems to show that as we are forced to push these studies further and further, the doses are going up, up, up. And what happens is that these doses get to so high a level, that they just lose any biologic meaning whatsoever.

Dr. Wurtman cited Dr. Garattini. Dr. Garattini's name is being taken in vain here. He does not agree with Dr. Wurtman. But I do agree with Dr. Wurtman that Dr. Garattini is a noted neuropharmacologist. But I think——

Dr. WURTMAN. Could I just respond to that, Senator?

Dr. FERNSTROM. Could I finish my point, Dick?

Senator METZENBAUM. I will let you respond in just a second.

Dr. WURTMAN. Fine, okay.

Dr. FERNSTROM. The point is that the whole thing must be based on biologic effects. And the point of the rest of my statement—which I guess is in the record and I will not get a chance to finish—is that as studies with aspartame get pushed further and further, the dose goes up, up, up, necessitating all sorts of incantations of how such high doses relate to humans. And in my estimation as a scientist working on aspartame, these high doses don't relate to humans.

[The prepared statement of Dr. Fernstrom follows:]

John D. Fernstrom, Ph.D.
Departments of Psychiatry
and Behavioral Neuroscience
University of Pittsburgh
Western Psychiatric Institute and Clinic
Pittsburgh PA

Senator Metzenbaum, Senator Hatch, thank you for inviting me to testify before this committee today.

My name is John Fernstrom. I am Associate Professor of Psychiatry and Behavioral Neuroscience in the Department of Psychiatry at the University of Pittsburgh. I have been on the faculty since 1982. Prior to joining the University, I was a faculty member at the Massachusetts Institute of Technology in the Department of Nutrition and Food Science for many years. My main area of research over the past 17 years has been on the effects of amino acids and the diet on brain neurotransmitter formation, an area that is relevant to today's discussion.

For today, the topic under discussion is aspartame, and in particular the phenylalanine contained in it. Phenylalanine is an amino acid that reputedly can influence neurotransmitter formation in brain, and because of this, someone with my research interests would be interested in exploring for such effects, in my case using rats.

Over the past five years, therefore, my laboratory has conducted a number of studies to determine whether aspartame ingestion can influence the formation of brain neurotransmitters in rats. At first, we used what then were considered high doses of aspartame, and found essentially no effects on neurotransmitter formation. These results were published in 1983 in a peer-reviewed journal. We then conducted further studies, using extremely large amounts of aspartame, and found some transmitter changes. However, we also found that the amounts of aspartame needed to produce such changes were extremely high, beyond anything that a human could ever consume. These results were also published, in the American Journal of Clinical Nutrition. We concluded that aspartame was really not a very interesting compound for producing transmitter changes. This conclusion fits with the fact that the phenylalanine in aspartame, which is the object of our studies, is an amino acid, not a drug. It should not be, and is not, a potent compound, like a drug.

Recently, it seems that investigators have lost sight of the fact that phenylalanine is a nutrient, not a drug, and have pressed ever higher doses into rats in search of effects. It is of notable interest that huge doses in rats are now discussed as being relevant to humans. In my opinion, this is silly. The requirement for ever higher doses simply infers that there really are no effects to be studied that could ever be relevant to normal human consumption. In a recent letter to the editor in the American Journal of Clinical Nutrition, I summed up my assessment by stating that:

"In sum, it is my opinion that this entire issue long ago transcended any scientific base that might ever have supported it. Enough is enough; it is time to move on. There are simply too many substantive issues that await investigation in the area of nutrition and brain function to waste further effort being obsessive about something that isn't there."

That something, of course, is any real effect of aspartame on brain function in rats or in humans.

Thank you for your time. I would be glad to answer any questions.

Senator METZENBAUM. Dr. Wurtman?

Dr. WURTMAN. Yes. Since my name was taken in vain—Dr. Garantini has published two papers and has two more in press—I know it, because I reviewed them—demonstrating the effects of aspartame in quite low doses, I think, in potentiating certain types of seizures in rats.

The key question has to be with what dose in the rat is comparable to a dose in the human. This is an area in which I think the FDA has not covered itself with glory. What they have done is to consider just the rate at which the body breaks down phenylalanine. And since the rate in the rat is about five times faster than the rate in the human, they have said, okay, to go from a rat dose to a human dose, divide by five.

We don't think that is the case, and I suspect, without having asked them, that these gentlemen would agree with me, that what counts is not simply the disappearance of phenylalanine, but also the appearance of its product, tyrosine, which is in many ways the antidote to the phenylalanine. And if one compares the rate at which the rat breaks down phenylalanine to tyrosine with the rate at which the human does it, then it is about a 50- to 60-fold difference. In that case, a 1,000 milligram per kilogram dose for a rat works out to about 15 or 16 milligram per kilogram for a human, which is really a quite low dose.

Now, I am not willing to hang from the neck until dead based on this 50- or 60-to-1 ratio. But I certainly do not think that a 5- or 10-to-1 ratio is intellectually valid, either. This is one of the areas in which much further research is needed, and quite quickly, because if it does turn out as I think, that a 1,000 milligram per kilogram for a rat or a mouse is a representative dose of a 7-year-old having, shall we say, two cans of soda, then we had really better know about it.

I had not planned to bring that up, but since Dr. Fernstrom mentioned the Garretini studies, I thought it would be appropriate to discuss it.

Senator METZENBAUM. Thank you, Dr. Wurtman.

I would like to ask a question. Isn't it correct that originally you believed that NutraSweet had no effects on the neurotransmitter formation—that was your first research on the brain chemistry—and then you conducted further studies and found that it did affect these transmitters in the brain? Is that correct?

Dr. FERNSTROM. Yes. The second series of studies differed from the first. In addition, one has to pay attention to the dose level at which effects were obtained. The dose level we were using in rats, which produced the threshold effect on brain neurochemistry, was over 500 milligrams per kilogram, a huge dose, administered as a single bolus. This work was published in the American journal of Clinical Nutrition in 1986.

The exact citation is: Fernstrom, JD, Fernstrom, MH, and Grubb, PE. Effects of aspartame ingestion on the carbohydrate-induced rise in tryptophan hydroxylation rate in rat brain. Amer. J. Clin. Nutr. 44: 195–205, 1986.

The point is that you are being told to buy a different set of goods, to buy a 60-fold conversion rate. That is really a very important point that you are being asked to buy: the implication is that low aspartame doses in humans should produce effects. But I think if you had a further set of panelists here, scientists who work in nutrition and in the metabolism of amino acids, that they would disagree with that point of view.

The article that is available to you that Dr. Wurtman has just published (Wurtman, RJ and TJ Maher. Effects of oral aspartame on plasma phenylatanine in humans and experimental rodents. J. Neural Transmission 70:169–73, 1987.) makes that 60-fold dose conversion, and I think the data that it is based on are highly suspect. They are not his. It is not a basic science article. It is a review article. And I think if you want to start arguing dose conversion, for my money, I take the nutrition and the metabolism community's conversion index of five, and I conclude that over 500 milligrams per kilogram converted to a human as a single dose is a huge dose. And I do not buy the 60-fold conversion that Dr. Wurtman is advertising now.

Senator METZENBAUM. You are a former student of Dr. Wurtman, is that correct?

Dr. FERNSTROM. Correct.

Senator METZENBAUM. Dr. Dews, you wanted to say something.

Dr. DEWS. I just wanted to comment, Senator, on the point you made about there are some doctors here who think one way, who are concerned, and there are some doctors who are expressing nonconcern, and it looks like it is about 3-to-2, and therefore we lose. I would like to point out for the record that in fact——

Senator METZENBAUM. I never said that.

Dr. DEWS [continuing]. There are 60 regulatory bodies in different countries around the world that have reviewed the same evidence as the FDA, the same evidence that we have reviewed, and have come to the conclusion that aspartame is safe for consumption.

You have already heard about the testimony of the entirely independent organizations such as the American Medical Association Council on Scientific Affairs, the American Academy of Pediatrics, Committee on Nutrition, the American Diabetic Association, and I think earlier, a number of other organizations. These are entirely independent organizations, representing a very large proportion of the physicians of the country in one way or another. They have set up panels that have carefully reviewed the evidence, and all of them have come to the conclusion that aspartame, as it is now consumed on the market, is safe. And to my knowledge, no such professional organization has come up with a different position.

Senator METZENBAUM. Dr. Dews, you say that NutraSweet has been approved all over the world without controversy. Let me quote from two articles of February 1984 in the British paper The Guardian. Quote:

> The head of the government committee responsible for approving the controversial new artificial sweetener aspartame, sold as Canderale and NutraSweet, has an indirect but significant link with the manufacturer G.D. Searle. The committee's decision, the Department of Health said at the time, was based on data supplied by the U.S. Food and Drug Administration (the FDA data consisted almost entirely of Searle's own research). Regulations legalizing its use in food and drink in the U.K. were laid before Parliament by the Junior Agriculture Administrator, Mrs. Peggy Fenner, during the summer recess, so they were not debated. Mrs. Fenner admitted

that she had been under commercial pressure to license aspartame quickly, because marketing arrangements were being held up.

Apparently, although approved, there seems to be some area of controversy.

Now, I just want to be certain about one thing. Dr. Dews, are you at this moment a consultant to ILSI?

Dr. Dews. Oh, indeed, yes, sir—from the very beginning, I have been.

Senator Metzenbaum. And you have always been a consultant to them?

Dr. Dews. From the beginning.

Senator Metzenbaum. And are you a consultant to NutraSweet as well?

Dr. Dews. No.

Senator Metzenbaum. Never?

Dr. Dews. Never.

Senator Metzenbaum. And Dr. Fernstrom, are you a consultant to ILSI?

Dr. Fernstrom. No, sir.

Senator Metzenbaum. How have your studies been funded?

Dr. Fernstrom. The only funds that I have gotten to do aspartame studies have been funded by the NutraSweet Company.

Senator Metzenbaum. By the NutraSweet Company.

Dr. Fernstrom. By the NutraSweet Company, that is right. I would point out, because of the laughs in the audience, that the result of all of our studies were submitted for peer review in scientific journals.

I would also point out that as a professor at MIT, I learned that one does not make any contracts or grants with any company unless one has full intellectual rights to all the information; and I took that attitude with me when I went to the University of Pittsburgh. And the fact of the matter is that I have full intellectual rights to anything I find with aspartame, and I will not do any studies unless they can be published in a peer review journal.

Senator Metzenbaum. Thank you very much. And I will say to the audience that I think witnesses are entitled to be heard with applauding or laughing or whatever; I think we ought to hear them on the basis of their own remarks.

Gentlemen, I would like to move this hearing along. I do have more questions, and we may submit them to you in writing. But your testimony has been very, very helpful, and thank you very, very much.

Our next witness is Dr. Jacqueline Verrett, Ph.D., Washington, DC.

Dr. Verrett, we are happy to hear from you.

STATEMENT OF DR. JACQUELINE VERRETT, FORMER TOXICOLOGIST, U.S. FOOD AND DRUG ADMINISTRATION, WASHINGTON, DC

Dr. Verrett. Thank you very much, Senator Metzenbaum.

I appreciate the opportunity of coming before you today, and perhaps I can straighten out what I think are some of the basic problems in this whole controversy, going back to the initial data that were received at Food and Drug.

Do we have time for me to read my whole statement?

Senator **Metzenbaum**. How much time will that take?

Dr. **Verrett**. I have not timed it, but probably seven minutes.

Senator **Metzenbaum**. That will be all right.

Dr. **Verrett**. From 1957 through 1977, I was employed as a biochemist/toxicologist in what is now designated as the Center for Food Safety and Applied Nutrition at FDA.

During this time, my duties were twofold—first, an evaluation of experimental data submitted to FDA in support of the safety of a wide variety of chemicals and processes such as irradiation that were intended for food additive use both directly and indirectly, as well as data pertaining to various contaminants in the food supply, such as mycotoxins and pesticides, and also of some drugs.

The second aspect of the work was a variety of research pertinent to FDA's mission and for the most part, devoted to the overall toxicity and more specifically to teratogenic—that is, birth-deforming—capabilities of several hundred substances that may be broadly classified as food additives or as food contaminants.

In the early 1970s, I examined the animal studies submitted by G.D. Searle on aspartame prior to the initial approval by FDA in 1974. While I cannot recall any specific examples, it was my overall impression that these studies raised numerous questions in a number of areas that needed to be resolved before approval of aspartame for any food additive use.

And this is not in my statement as written, but I would like to add here to make things clear, the fact that the initial submission to which I am referring as were most petitions submitted to Food and Drug, was in a summary form. We did not see individual records and so forth, and it already had conclusions drawn.

In 1977—and this is after the investigation of Searle—I served as a member of an FDA team from the Bureau of Foods which was charged with examining three studies—specifically, the rat long-term study of the DKP, diketoperpazine, which is a breakdown product of aspartame—and two aspartame teratology studies in mice and rats. We were doing this to determine if they were authentic.

We were instructed to incorporate the findings of the FDA task force investigation—which I will refer to now as the Bressler Report—and to determine whether alterations and adjustments to the data engendered by the inclusion and consideration of all of these discrepancies resulted in any significantly different results from those originally presented in the original Searle submission.

This authentication was hence intended to verify that the submitted data had not been altered; that it reflected the actual outcome of the study, and that it did not change substantially, particularly in a statistical sense, the various parameters from which the conclusion of safety had been derived.

Our analysis of the data in this manner revealed that in these three studies, there were really no substantial changes that resulted, although in numerous instances, a definitive answer could not be arrived at because of the basic inadequacies and improper procedures used in the execution of these studies.

I would like to emphasize the point that we were specifically instructed not to be concerned with, or to comment upon, the overall validity of the study. This was to be done in a subsequent review, carried out at a higher level.

It is apparent that the review, on a point-by-point basis, that was done later discarded or ignored the problems and the deficiencies outlined in this team report and concluded that, even in toto, all of these problems were insufficient to render the study invalid.

It also appears that the serious departures from acceptable toxicological protocols noted in the reevaluations of these studies were also discounted.

At this point it might be helpful to mention some of these deficiencies and improper procedures that were encountered:

(1) There was no protocol written until the study was well underway; (2) Animals were not permanently tagged to avoid mixups over the course of the study; (3) Changes were introduced in some laboratory methods during the study with inadequate documentation; (4) There was either sporadic or inadequate reporting and monitoring of both feed consumption and animal weights; (5) In some cases, tumors were removed, and the animals then returned to the study; (6) Animals were recorded as dead and then subsequent records, after varying periods of time, indicated the same animal was still alive—almost a certain evidence of mixup; (7) Many animal tissues, a significant number, were autolyzed, that is, decomposed, before any post mortem examinations were performed; (8) And finally, of extreme importance is that in the DKP study there was evidence, including pictures found in notebooks at Searle, that the diets were not homogeneous, and that the animals could discriminate between feed and the included particles of DKP. In other words, they may or may not have been eating what it was assumed they were eating.

Almost any single one of these aberrations would suffice to negate a study designed to assess the safety of a food additive, and most certainly, a combination of many such improper practices would, since the results are bound to be compromised.

It is unthinkable that any reputable toxicologist giving a completely objective evaluation of this data resulting from such a study could conclude anything other than that the study was uninterpretable and worthless and should be repeated. This is especially important for an additive such as aspartame, which, as we have heard already today is intended for and is now being used in such a widespread and uncontrolled fashion.

It is equally vital, since this DKP, the subject of the study that I am referring to, is a major breakdown product of aspartame in liquid media.

So what we essentially have is that not only is aspartame being used in the absence of basic toxicity information, but there is also no data to assess the toxicity of interactions of this DKP with excess phenylalanine, with any other metabolite of aspartame, or with interactions of other additives, drugs or other chemicals, which may be simultaneously present in persons exposed to high levels of DKP in pre-sweetened liquids such as diet drinks.

While I have not been involved in safety matters concerning aspartame since this team effort described some time ago, a brief examination of studies completed and currently underway seems to indicate that the subject studies have not been repeated, so the safety questions, and hence the acceptable daily intake figures that were derived from them remain in question and remain unanswered.

It would appear that the safety of aspartame and its breakdown products has still not been satisfactorily determined, since many of the flaws cited in these three studies were also present in all of the other studies submitted by Searle.

That is the end of my statement, Senator. Thank you.

Senator **METZENBAUM**. Thank you very much, Dr. Verrett.

Dr. **VERRETT**. I should say that I also did a literature survey of the NIH/NLM Libraries. I have brought that with me. It is not organized, but I think it might be of some help to you in determining exactly what has been done. In a quick scan of it, I do not find studies that repeat any of this research enough to answer the questions that were raised.

Senator **METZENBAUM**. So that many of the studies that have been reported subsequently were based upon the findings of the original study, and the original study is the one that you found so flawed?

Dr. **VERRETT**. That is correct. That sort of applies to some of the discussion that you had recently. Many other countries, in evaluating the data, did not actually evaluate the raw data. They accepted the fact that Food and Drug had found it safe. They did not have the opportunity to look at the raw data and to see the flaws in the basic experiments that were done.

Senator **METZENBAUM**. Dr. Verrett, you are a Ph.D.?

Dr. **VERRETT**. Yes. I have a Ph.D. in biochemistry from Fordham University. I have also degrees in physical chemistry as well. My first full-time job, actually, was with Food and Drug. I left there about nine years ago, and I am now employed as a consultant, primarily with EPA.

Senator **METZENBAUM**. Did you know there were nearly 170 studies submitted to the FDA to prove NutraSweet's safety; of those, 9 were crucial to safety. You reviewed, really, the basic one, the long-term DKP study.

Dr. **VERRETT**. Yes, that was one of the so-called critical. And the other two——

Senator **METZENBAUM**. Why is that important? Why is that so important?

Dr. **VERRETT**. Because it was recognized even then that DKP is formed to a large extent when liquids in particular are presweetened with aspartame. Its production is also very much subject to increases in temperature. And based on the information that was presented at that time—and I think to some extent that has been reinforced—the higher the temperature, the more of this DKP that is formed; in other words, sitting on the shelf, we are getting this compound formed.

And incidentally, in spite of the sweetness of aspartame, because of its decomposition in liquids, I have read that a majority of the diet drinks, and other products of that nature, use somewhat more than would really be necessary for sweetening in order to compensate for this decomposition over a long shelf life.

So it is acknowledged, and that is why initially, aspartame was not intended or not planned to be used in liquids because of this decomposition.

Senator METZENBAUM. The first study that was made—was this at the time that dry substance was being talked about?

Dr. VERRETT. The study that I am talking about?

Senator METZENBAUM. Yes.

Dr. VERRETT. Yes, of course. This was a dry mixture of solid DKP crystals into the animals' diet. This was not a study of it in drinking water or anything like that.

Senator METZENBAUM. There was no mention of taking it in the quantities that it is now ingested in liquid form, so that the original studies were made when it was contemplated that there would be a very limited ingestion of DKP in——

Dr. VERRETT. I am not sure I can answer that accurately, Senator. The thing is that I think it was initially proposed for both uses, but that with the data that were generated on its breakdown to DKP and so forth, that it was decided that it was too unstable to be used in hot preparations, hot liquids, and also in diet drinks. And it was only later that those uses were added. First, the approval in 1974 was strictly for dry foods. Even that, on the basis of what I am describing here, was based on relatively questionable data.

In other words, we really do not know with any degree of certainty, as far as I can see, that this ADI and these other figures we are talking about have any meaning whatsoever, because the quality of these critical studies in which animals were fed these materials for one, two years, and so forth, was such that any kind of calculation of a no-effect level, if you wish, in that study, which is used to develop the ADI, cannot have any degree of accuracy about it. And the problems in this research—and these are not all of them but, I have listed some of the most serious—but the problems in this study were common to all of the studies in some degree. And I should say it leaves a huge question about teratology, birth defects, things that have been discussed by other panelists.

Those two teratology studies that I reviewed, in addition to the DKP that my panel looked at, were also woefully inadequate.

Senator METZENBAUM. Dr. Verrett, let me quote to you from a Searle Company memo dated December 28, 1970. The author was Mr. Helig, and in the memo he talks about their strategy for getting NutraSweet approved: "The basic philosophy of our approach to Food and Drug should be to try to get them to say 'yes', too, even if we have to throw some in that have no significance to us other than putting them into a 'yes'-saying habit. We must create an affirmative atmosphere in our dealing with the FDA. It would also help if we can get them, or get the people involved, to do us any sort of favor, as this would also bring them into a subconscious spirit of participation. My prime concern at this time is with the production of aspartame and our lack of complete toxicological data on DKP."

How do you react to that?

Dr. VERRETT. My first reaction is that I am not at all surprised. I had not been aware of this, of course, before. And I do not want to imply that there was anything dishonest in this submission or others that I have had dealings with. But I have been involved with a number of the industries, read many of their petitions, and it seems to me that they do use pressure because they themselves maybe are really convinced that there is nothing wrong with these things.

And I have been to many a meeting where that kind of approach which was suggested there was used. It is obvious we were being conned, or put in a mental state of thinking we didn't have a problem, before we ever read the data. Now, I am not saying this was dishonest, either. And this data certainly seemed to be an honest admission. You know, it wasn't manipulated. Certainly, if anybody had tried to make this up, they couldn't have; they would have had to do it better.

So I do feel in my 20-year experience there, to the extent that I had to deal with representatives of industry, many of whom I have a very high regard for, certainly, but that there is a subtle pressure, brainwashing, if you wish, and one does have to go through this sort of data with a fine-toothed comb.

Now, admittedly, some of the procedures that are currently used now were not always used. One of the problems here was that we accepted, not only from Searle but from everybody, summarized data. We had no way of knowing the fact that animals died and were being resurrected, missing, mixed up, all of this, until something called attention to it. And I should say that in this case aspartame was not the only substance that was being investigated at Searle. It happened at that time there were also two drugs for which there were apparent problems, so inspectors went in and, I think, looked over a series of things, one of them, aspartame, being the food additive that was chosen.

But the problem is that even had this study been done perfectly—if there is any such thing—if they had followed the protocol—interpretation of the results would not have been clear-cut. We did not even in that day, need the good laboratory practices; the GLP regulations are helpful, and we tell people exactly what to do now, but any high school pupil or high school teacher with common sense would know that you have to identify your animals individually, otherwise you cannot tell them apart. All white rats look alike. And some of the deficiencies maybe trivial, if you want to say that, on an individual basis; this is exactly the way the investigating committees or whatever they were that examined these studies after my task force did, that is exactly the way they treated them. All of the deficiencies that we pointed out on a one-by-one basis, they quietly said, "Oh, that is not that important of itself," and then they promptly dismissed all 25 or 30 of them in toto, after having said each one was irrelevant.

They even contradicted themselves. This (DKP) is the famous study with the uterine polyps, and it is also the study in which there were changes in serum cholesterol, significant changes over the dose range.

Now, we still are not sure exactly how much of DKP each group of animals or any individual animal got; they may not have gotten what would be calculated on the basis of daily consumption had the diet been homogeneous.

The fact is, in spite of that, there were significant increases—and I think everybody agrees with that—of uterine polyps and also changes in blood cholesterol.

When that was then taken into consideration, they said, oh, well, obviously, they must have gotten the diet, because we have these changes. But then they disregarded the changes as being significant—you know, uterine polyps were not pre-carcinogenic. Well, I can rustle up 15 million women by this afternoon who will disagree with that.

Senator **Metzenbaum**. Would you say, generally speaking, the whole basis of approving NutraSweet as related to the DKP study that came before you was invalid?

Dr. **Verrett**. Not only the DKP study. I feel that some of the other studies of aspartame—I read the others as well, although the memo specified that we analyze the DKP study—and the two studies on teratology,—I feel that as a minimum, they are seriously flawed because of enough problems in the way they were conducted that it makes it difficult to interpret them and come up with any kind of a figure in which we could have confidence for an ADI.

And of course they certainly did nothing to deal with the other issues that have been discussed here today, such as effect of phenylalanine excess on the brain or other neurotoxic effects; these are simply crude, "rough-and-dirty", if you wish, hammer-and-tongs approaches—feed in excess and see what effects you get. There was nothing in them to look at the metabolism, to find out what it was breaking down into. These are just the basic things to try to find out what is the toxic dose to a rat or mouse, and I feel we really do not have that yet with any certainty.

Senator **Metzenbaum**. As a Ph.D. toxicologist for 20 years in the FDA, and as someone who as examined the scientific validity of this test, apparently, you would totally disagree with the Commissioner's statement that he has complete faith in the credibility of tests used to approve the product.

Dr. **Verrett**. I do disagree with that, I am sorry to say.

Senator **Metzenbaum**. You do disagree.

Dr. **Verrett**. Yes, because if it is these studies—and I am limiting my comments on the submission by Searle—I do not feel that they provide us any information, or let us say, they do provide some information, but there are so many problems such as those that I cited in not only this DKP, but in the others as well, that we cannot come up with any assurance that we have the right ADI.

Senator **Metzenbaum**. You are quoted in a recent UPI story as saying that you just wanted to come out and say that this whole experiment was a disaster and should be discarded. What stopped you? Were you restricted in any way?

Dr. **Verrett**. Well, they told us in no uncertain terms that we were not to comment on the validity of it. And I hoped, although having been there at that point for 19 years, I should have known better, that there really would be an objective evaluation of this beyond the evaluation that we did.

I do not feel that that was done, based on what I have read in the GAO report that I have looked at and so forth. They definitely did not objectively evaluate these studies, and I really think it should have been thrown out from day one.

We were looking at a lot of little details and easy parameters in this study, when the foundation of the study, the diet and all of these other things, were worthless. We were talking about the jockey when we should have been talking about the horse, that he had weak legs. It is built on a foundation of sand.

Senator METZENBAUM. Do you think we should repeat the test?

Dr. VERRETT. I feel it, yes, unless—I am unaware of some that have been done, and that were done properly, and would give us some assurance of being able to calculate these values that we need. But I have no qualms in saying that if we are basing the amount of aspartame that we are putting in all of these foods today on these studies, then it is a disaster.

Senator METZENBAUM. Thank you very much, Dr. Verrett. Your testimony has been very helpful.

Dr. VERRETT. Thank you, Senator, for having me testify.

Senator METZENBAUM. Next we will hear from a representative of the American Diabetes Association, Dr. Xavier Pi-Sunyer.

We are happy to have you with us, Doctor.

STATEMENT OF DR. F. XAVIER PI-SUNYER, MEMBER, AMERICAN DIABETES ASSOCIATION BOARD OF DIRECTORS, ALEXANDRIA, VA

Dr. PI-SUNYER. How do you do, Senator? My name is Xavier Pi-Sunyer. I am Professor of Clinical Medicine at Columbia University, and head of the Division of Endocrinology and Diabetes at St. Luke's Roosevelt Hospital in New York City.

I am also a member of the American Diabetes Association Board of Directors, and I am here representing them. The ADA is pleased to submit its views on aspartame to the Committee on Labor and Human Resources.

ADA is the Nation's leading voluntary health organization representing the interests of over 11 million Americans with diabetes. Our policies and position statements are developed within an organization of approximately 5,000 physicians and scientists, 2,500 health care professionals, and over 200,000 patients. We publish the two largest scientific journals in the field of diabetes in the world.

ADA's mission is to find a preventive and cure for diabetes and to improve the well-being of all people with diabetes and their families.

Diabetes is a disease in which the body does not produce or properly use insulin, a hormone needed to convert foods into the energy needed for daily life. Normally during digestion the body changes sugars and starches and other foods into a form of sugar called glucose. The body carries this glucose to cells throughout the body and there, with the help of the hormone insulin, which is made in the pancreas, glucose is changed into energy for immediate use by the cells, or is stored for future needs. This process of turning food into energy is crucial, because the body depends on food for every action, from pumping blood and thinking to running and jumping.

In diabetes, something goes wrong with the normal process of turning food into energy. Food is changed into glucose readily enough, but there is a problem with insulin. In Type I diabetes, which usually occurs in children and young adults, the pancreas cannot make insulin, so insulin must be injected every day. In Type II diabetes, which usually occurs in adults over 40 and is a particular problem for persons who are obese, the body makes some insulin, but either makes too little or has trouble using the insulin it makes. Treatment for non-insulin-dependent diabetes includes exercise and a meal plan to control weight.

The major aim of treatment of diabetes is to control the blood-glucose level. A diet which limits sugar is crucial to the treatment of both types of diabetes. The 11 million Americans with diabetes rely on sweeteners such as aspartame as an alternative to the use of sugar. These products make it easier for people with diabetes to comply with their diets and still enjoy their food.

ADA, through its publications and other activities, communicates with the majority of physicians who treat people with diabetes. Through the journal Clinical Diabetes alone, we are in regular contact with approximately 70,000 physicians who are actively involved in the care of patients with diabetes. We have had no indication from these professionals that there are significant problems with the use of aspartame or, for that matter, that there is any pattern of complaints regarding this product.

The use and safety of aspartame simply has not been an issue among these health professionals as far as we can determine.

ADA's National Service Center Patient Information Hotline receives 8,000 to 10,000 calls a year, and we maintain a record of what people call about. Less than one percent of our calls are on the topic of any of the artificial sweeteners, despite the sometimes misleading public press articles that arise from time to time.

ADA affiliates around the country, which receive an even larger number of calls from people with diabetes, have also reported no problem with complaints about aspartame.

Our position statement on the use of sweeteners was approved on March 6, 1987. This statement represents broad and expert scientific opinion based on a review of published scientific studies. It states that ADA believes that although safety concerns have been raised regarding aspartame, aspartame has been determined to be safe for the general population as well as for people with diabetes.

This has been reaffirmed in ongoing evaluations by the FDA, as well as by the recent GAO study. ADA feels aspartame is safe when used at the levels established as acceptable. We believe the most recent studies published do not provide sufficient data to warrant discontinuation of aspartame.

In addition, ADA recommends that further research be conducted to go beyond our current knowledge regarding artificial sweeteners. We do not believe, however, further studies are needed to duplicate current knowledge.

Part of ADA's mission is to improve the quality of life for all people with diabetes. Aspartame helps achieve this by being a noncaloric sweetener that tastes good and can be used in many products. Sweeteners are important for people with diabetes for improving their dietary control of blood sugar. If artificial sweeteners were not available, it would be more difficult for many of the millions of people with diabetes to maintain a proper diet.

In conclusion, ADA supports the continued availability of aspartame. Our organization believes the product has been shown to be safe.

The ADA is also concerned about the impact of this hearing and the corresponding publicity on the patient population we represent. Current efforts should avoid the undesired outcome of raising unwarranted anxiety among people with diabetes. We urge that Congress focus its attention on the broad evidence of science and nutrition, not on unrepresentative, individual anecdotal assertions.

We ask the Committee to bring a final dispassionate resolution to this issue as swiftly as possible.

Thank you again for the opportunity to share the views of the ADA.

[The prepared statement of Dr. Pi-Sunyer follows:]

American Diabetes Association., Inc.

National Service Center 1660 Duke Street Alexandria, Virginia 22314 (703) 549-1500 Telex: 901132

STATEMENT

OF THE

AMERICAN DIABETES ASSOCIATION

SUBMITTED TO THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

UNITED STATES SENATE

ON

ASPARTAME

WITNESS: F. Xavier Pi-Sunyer, M.D.
Professor of Clinical Medicine,
College of Physicians & Surgeons,
New York
Chief, Diabetes Clinic
Chief, Division of Endocrinology
and Diabetes
Associate Director, Obesity Research
Center, St. Luke's Roosevelt
Hospital Center
Department of Medicine
New York, New York

Member, ADA Board of Directors

November 3, 1987

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The American Diabetes Association (ADA) is pleased to submit its views on aspartame to the Committee on Labor and Human Resources. ADA is the nation's leading voluntary health organization representing the interests of over 11 million Americans with diabetes. Our policies and position statements are developed within an organization of approximately 5,000 physicians and scientists, 2,500 health care professionals, and over 200,000 patients. We publish the two largest scientific journals in the field of diabetes, as well as several magazines, books and newsletters. ADA's mission is to find a preventive and cure for diabetes, and to improve the well-being of all people with diabetes and their families.

Diabetes is a disease in which the body does not produce or properly use insulin, a hormone needed to convert foods into the energy needed for daily life. Normally, during digestion, the body changes sugars, starches, and other foods into a form of sugar called glucose. Then the body carries this glucose to cells throughout the body. There, with the help of insulin which is made in the beta cells of the pancreas, glucose is changed into quick energy for immediate use by the cells or is stored for future needs. This process of turning food into energy is crucial, because the body depends on food for every action, from pumping blood and thinking to running and jumping.

In diabetes, something goes wrong with the normal process of turning food into energy. Food is changed into glucose readily enough, but there is a problem with insulin. In Type I diabetes, which usually occurs in children and young adults, the pancreas cannot make insulin. Since insulin is necessary to life, the hormone must be injected every day. In Type II diabetes, which usually occurs in adults over 40 and is a particular problem for persons who are obese, the body makes some insulin but either makes too little or has trouble using the insulin it makes. Treatment for non-insulin dependent diabetes includes exercise and a meal plan to control weight.

The major aim of treatment of diabetes is to control blood-glucose levels. A diet which limits sugar is crucial to the treatment of both types of diabetes. The 11 million Americans with diabetes rely on noncaloric sweeteners, such as aspartame, as the principal alternative to the use of sugar. These products make it easier for people with diabetes to comply with their diets and still enjoy their food.

ADA, through its publications and other activities, communicates with the majority of physicians who treat people with diabetes. Through the journal Clinical Diabetes alone, we are in regular contact with approximately 70,000 physicians who are actively involved in the care of patients with diabetes. We estimate that these physicians -- who regularly receive medical information from our Association -- receive a minimum of 5,000,000 patient office visits per year from people with diabetes. The vast majority of these physicians and patients have information about the ADA's telephone hotline, 1-800-ADA-DISC. We have had no indication from these professionals that there are significant problems with the use of aspartame, or for that matter, that there is any pattern of complaints regarding this product. The use and safety of aspartame simply is not an issue among these health professionals, as far as we can determine.

ADA's National Service Center's Patient Information Hotline receives 8,000 to 10,000 calls a year, and we maintain a record of what people call about. Less than 1% of our calls are on the topic of any of the artificial sweeteners, despite the sometimes misleading public press articles that arise from time to time. ADA affiliates, which receive an even larger number of calls from people with diabetes, have reported no problem with complaints about aspartame.

ADA's Executive Committee approved our position statement on the use of noncaloric sweeteners on March 6, 1987. A copy of the statement is attached. This statement was prepared by our council on Nutritional Sciences and Metabolism, and represents broad and expert scientific opinion based on a substantial and current review of published scientific studies. It states that ADA believes that although safety concerns have been raised regarding aspartame, aspartame has been determined to be safe for the general population as well as for people with diabetes. This has been reaffirmed in ongoing evaluations by the Food and Drug Administration (FDA) as well as by the recent General Accounting Office (GAO) study. ADA feels aspartame is safe when used at the levels established as acceptable. We believe the most recent studies published do not provide sufficient data to warrant discontinuation of aspartame.

In addition, ADA recommends that further research be conducted to go beyond our current knowledge regarding artificial sweeteners. We do not believe further studies are needed to duplicate current knowledge.

Part of ADA's mission is to improve the quality of life for all people with diabetes. Aspartame helps achieve this by being a noncaloric sweetener that tastes good and can be used in many products. Noncaloric sweeteners are important for people with diabetes in improving their dietary control. If artificial sweeteners were not available, it would be more difficult for many of the millions of people with diabetes to maintain a proper diet.

In conclusion, ADA supports the continued availability of aspartame. Our organization, which has ongoing contact with a major portion of the diabetic population using aspartame and the physicians who treat them, believes the product has been shown to be safe.

The ADA is concerned about the impact of this hearing and the corresponding publicity on the patient population we represent. Current efforts should avoid the undesired outcome of raising unwarranted anxiety among people with diabetes. We urge that the Congress, the Administration and the press focus their attention on the broad evidence of science and nutrition, not on unrepresentative individual anecdotal assertions. We ask the Committee to bring a final dispassionate resolution on this issue as swiftly as possible.

Thank you again for the opportunity to share the views of the ADA.

Position Statement

Use of Noncaloric Sweeteners

AMERICAN DIABETES ASSOCIATION

Many people with diabetes restrict the amount of refined sugars (e.g., glucose and sucrose) in their diet. Consequently, noncaloric sweeteners are often used. There are two federally approved noncaloric sweeteners, saccharin and aspartame. Concerns related to saccharin and aspartame use have focused on their safety.

Saccharin. A small risk for bladder cancer continues to be associated with high-dose consumption of saccharin in certain laboratory animals. However, epidemiological studies show no evidence of a carcinogenic effect in humans. Although the question of carcinogenicity of saccharin for humans cannot be completely ruled out, the risk, if any, from ingestion at moderate levels is considered to be extremely small. Because saccharin can cross the placenta, heavy use during pregnancy should be avoided.

Aspartame. Aspartame (a protein sweetener composed of two amino acids) is technically a nutritive or caloric sweetener; however, it is so sweet that it is effectively noncaloric in the amounts normally consumed. Various safety concerns have been raised in regard to aspartame. Nonetheless, aspartame has been determined to be safe for the general population as well as for people with diabetes. This has been reaffirmed in ongoing evaluation by the Food and Drug Administration.

Based on available evidence, the American Diabetes Association finds the use of the two commercially available noncaloric sweeteners saccharin and aspartame to be acceptable (1). The following are additional recommendations:

1. The use of both sweeteners (saccharin and aspartame) is encouraged for the particular advantages of each.

2. The use of aspartame and saccharin should be within the levels established as acceptable.

Ingestion of 50 mg aspartame · kg^{-1} body wt · day^{-1}, which is ~1% of the amount shown in animals and humans to have no toxic effects, has been established as the lifetime acceptable daily intake (ADI) for aspartame by the Food and Drug Administration. An intake of 50 mg · kg^{-1} body wt · day^{-1} is equivalent to the daily consumption of ~17 12-oz cans of a 100% aspartame-sweetened soft drink by a 70-kg (154 lb) person. The usual level of aspartame consumption is well below this amount. For example, data indicate that <10% of adults consume aspartame in amounts >3.5 mg/kg body wt, and <10% of children 2–5 yr old consume >11 mg/kg body wt on days in which aspartame was ingested.

As established by the 1955 GRAS (Generally Recognized As Safe) list of recommendations, an intake of 500 mg/day of saccharin for children and ~1000 mg/day for adults is acceptable. One teaspoon (one packet) of saccharin powder, which includes a buffer, contains 14–20 mg of saccharin. Thus, a child could consume ~25–35 packets/day, and an adult could consume 50–70 packets/day. No other limitations for saccharin use have been established. Actual consumption levels of saccharin are likely to be considerably below these levels.

3. The food industry is encouraged to label products with the amounts of noncaloric sweeteners present, as it should all food ingredients. Labeling should include the amount of each ingredient in milligrams per serving and the number of servings per container.

4. We encourage continued research to rule out any suspected risks as well as to determine the metabolic effects of long-term individual and combined sweetener use in diabetic people. The contribution of noncaloric sweeteners to diabetes control and to weight reduction also merits further investigation.

In conclusion, the dietary needs of people with diabetes vary, and the use of any sweetener should be individualized with consideration to overall diet and nutritional adequacy. The American Diabetes Association recommends that people with diabetes consult a nutritionist, physician, or health-care professional knowledgeable about diabetes nutrition management concerning the amount and source of sweeteners in their daily meal plans.

The recommendations were approved by the American Diabetes Association Executive Committee, 6 March 1987, and prepared by a task force of the Council on Nutrition Sciences and Metabolism:

Phyllis Crapo, RD, Task Force Chairperson
Frank Nuttall, MD, Council Chairperson

REFERENCE

1. American Diabetes Association: Nutritional recommendations and principles for individuals with diabetes mellitus: 1986. *Diabetes Care* 10:126–32, 1987

Senator METZENBAUM. Thank you very much, Dr. Pi-Sunyer.

As I understand your testimony, you support labelling to indicate the amount of content; is that correct?

Dr. PI-SUNYER. Yes. I think the ADA has always supported that.

Senator METZENBAUM. And second, you support additional continued research to rule out any suspected risks as well as to determine the metabolic effects of long-term individual and combined sweetener use in diabetic people; and third——

Dr. PI-SUNYER. Well, can I comment on that?

Senator METZENBAUM. Surely.

Dr. PI-SUNYER. I think we are in favor of further research if it is new research. I think the priorities for research monies are very tight. We personally are interested in diabetes and in finding a cure for diabetes. I think there are priorities about where research dollars go, and I think it would be too bad to spend money on work that has already been done. But new research, I think we would certainly be in favor of.

Senator METZENBAUM. I notice you said research already done. You have just heard Dr. Verrett testify to the research that was done on her watch, in which she said it just was totally inaccurate, and the facts were confused. Don't you think that a redoing of that particular research project would be warranted?

Dr. PI-SUNYER. Well, Senator, I also heard the Commissioner of the FDA saying that he felt the studies were adequate. I also have read the GAO examination of that whole issue, and although I am not an expert on what went on in the FDA over the past 15 years, we have gotten some testimony to the effect that the studies were adequate.

Dr. Wurtman said there were no clinical studies—but there have been clinical studies done on the safety of aspartame and its use in diabetics.

Senator METZENBAUM. The GAO said, "We did not evaluate the scientific issues raised concerning the studies used for aspartame's approval or FDA's resolution of these issues, nor did we determine aspartame's safety."

I have difficulty, Doctor, in understanding your saying that you do not think it ought to be redone under those circumstances and question why the ADA, which is such a well-respected organization, would not be in favor of being certain that the millions of diabetics who are using aspartame can be reassured that aspartame is indeed safe and that the studies that were done and were done under obviously perverted circumstances, as testified to by Dr. Verrett——

Dr. PI-SUNYER. Well, we are a private voluntary organization. We do not have a research arm. We do give research monies out for grants. We are interested in the well-being of the diabetic. And therefore, anything that impacts on their care or safety, we are interested in.

In our reading of what has gone on, and with the amount of aspartame used today, and with the kinds of pipelines we have to physicians who treat diabetics and to the public who are diabetics, who are members of our organization, we have not found in those particular items that there is a major problem.

Now, the Commissioner of the FDA also seems to feel there is not a major problem. In addition, we are not the only voluntary organization that has done this. The American Academy of Pediatrics has said the same thing. They have a panel that said that this seems to be reasonable as far as they are concerned. The American Medical Association has done the same thing, as well as the Epilepsy Institute. There are a number of organizations that have tried to look at the data as best they can and who have pipelines to people who might be at risk and have not been able to come up with a great number of safety problems with this product which is being used by a very great number of people in the United States today, and in fact around the world.

Senator **Metzenbaum**. Well, I do have more questions for you, Doctor, because I do have some reservations about your testimony and the position that you have taken. It seems to me that we all agree—and I do agree strongly with your comment—that diabetics should not be alarmed and others who use aspartame for purposes of not ingesting sugar; that they should not be alarmed by these hearings. But when you indicate some concern about going forward with further studies, when I have a whole panel of——

Dr. **Pi-Sunyer**. No, no. I said I was in favor of further studies, Senator.

Senator **Metzenbaum**. Okay. Well, thank you very much, Dr. Pi-Sunyer.

Our next and last witness—and I want to make it clear that he was the last witness by request; it was not because we did not think his testimony was particularly important to this Committee—is Dr. Robert Shapiro, President of the NutraSweet Company.

We are happy to have you with us, Doctor. We have met on many occasions before.

STATEMENT OF ROBERT SHAPIRO, CHAIRMAN OF THE BOARD AND CHIEF EXECUTIVE OFFICER, NUTRASWEET COMPANY, WASHINGTON, DC

Mr. **Shapiro**. Thank you, Senator, and thank you also for conferring a doctorate on me. I appreciate it.

Senator **Metzenbaum**. All right. I take it back. Correct the record. Mr. Robert Shapiro.

Mr. Shapiro, how much time do you think you will need?

Mr. **Shapiro**. Oh, perhaps eight or ten minutes, Senator.

Senator **Metzenbaum**. Fine.

Mr. **Shapiro**. With your permission, I have a prepared statement which I have submitted for the record.

Senator **Metzenbaum**. Fine. It will be included in the record.

Mr. **Shapiro**. Thank you. I would like to make a brief statement now.

Before doing that, I have been informed by staff that the Food and Drug Administration plans to submit to the Committee a point-by-point rebuttal of a number of the statements that have been made by the witnesses here today subsequent to the FDA's testimony. And I certainly look forward to seeing that.

Much of what the Committee has heard today, in all its complexity, seems to me to boil down to a single proposition: The FDA is simply wrong, not once, but repeatedly, when it has affirmed and reaffirmed and reaffirmed the safety of aspartame.

Now, of course, anyone is entitled to disagree with a Government agency. But it is critically important to note that on this subject the FDA does not stand alone. In attacking the FDA, those who attack the safety of aspartame are also attacking the independent determinations of the health and regulatory authorities of the world.

The fact is, Senator, that every single authoritative scientific, medical and regulatory body in the United States and around the world that has ever examined the scientific evidence on the safety of aspartame has each, independently and separately, arrived at a single identical conclusion, and that is that aspartame is safe.

Senator **Metzenbaum**. Can you tell me how many of those were based upon independent research and how many were just based on the fact that it had been approved by the FDA or somebody else?

Mr. **Shapiro**. I know of no advanced nation in the world in which an approval of the FDA is regarded as sufficient to allow a new entity to be admitted into the food supply of that nation.

Each nation has created an elaborate and detailed regulatory process which examines all the scientific evidence that is known and reaches a separate, independent conclusion.

Now, there are, I am told, some countries of the less-developed world which lack those processes and simply accept the approvals of more advanced nations. But that certainly is not true, for example, of Canada, England, the Scandinavian countries, Germany, France, Switzerland, Japan, Australia—all the countries which have separately and independently looked at the same data the FDA has, looked at all the scientific evidence available, and reached the identical conclusion.

Now, it may be that the FDA is wrong, but if they are wrong, so is the entire world scientific and regulatory community.

In addition to those regulatory agencies, Senator, the subject has been examined by the Joint Expert Committee on Food Additives of the World Health Organization, by the Scientific Committee for Food of the Commission of the European Communities, by the Council on Scientific Affairs of the American Medical Association, by the American Academy of Pediatrics, by the Epilepsy Institute and so on. All have reviewed the evidence and, contrary to some of the witnesses today, all have arrived at the same conclusion.

What is remarkable as I listen to today's testimony, in the context of the world's conclusions on this subject, what is truly remarkable is not what was heard today; what is remarkable is the unanimity and uniformity of the worldwide scientific consensus as to the safety of aspartame.

In the face of that, why have we heard today testimony which seeks to create an impression of scientific controversy on that subject?

The testimony we have heard repeats once again in this forum three themes that have repeatedly been examined and found to be without merit.

The first theme consists of criticisms of the FDA approval processes, either as a general proposition or with respect to aspartame in particular. Those criticisms have been reviewed initially in Mr. Turner's submissions to the Food and Drug Administration; subsequently, in his appeal to the Circuit Court for the District of Columbia which, in a unanimous opinion written by Judge Abner Mikva, rejected Mr. Turner's objections to the approval of aspartame and upheld the FDA's approval of aspartame. And most recently, that process has been reviewed at your request by the General Accounting Office of Congress which, as has been repeatedly noted today, vindicated the FDA's following its processes.

Now, it is perfectly possible to argue that other processes are more appropriate, that legislation should be introduced to change the FDA's processes. But the fact is that those processes were followed.

And all we have heard today is a repetition of the same set of issues that were looked into by the courts, by the FDA, and by the GAO.

Indeed, in this context, it is again significant that the FDA does not stand alone. If there is something wrong with the FDA and with its approval process, the same thing must be wrong in Canada and England and Germany and Switzerland and all the other nations of the world which, using their independent and separate processes, have come to the identical conclusion that the FDA has.

The second theme of the testimony you have heard today rests on anecdotal complaint. I have addressed the subject in my written testimony, and Commissioner Young addressed it, I believe, in his testimony—the question of the reliability and significance of anecdotal reports such as you have heard today. I would only point out now that whenever such claims have been scientifically investigated, whether by the Centers for Disease Control, the FDA, or by focused clinical studies, no correlation has been found between aspartame consumption and the symptoms complained of.

The statement of Dr. Bennett Shaywitz, of the Yale University School of Medicine, which I understand Senator Hatch submitted for the record earlier, is, I think, directly relevant to that issue, and I only want to quote one brief paragraph from it.

Dr. Shaywitz says, "In my personal evaluation and research, I have found no clinical evidence in humans nor any other reason to believe that there is a relationship between aspartame consumption and seizures."

It is also, I think, instructive to note that when subjects who believed that they had headaches caused by aspartame consumption, and if they could demonstrate a relationship in time between aspartame consumption and a headache incident, and could demonstrate that that had occurred not once, but repeatedly, when such subjects were exposed to aspartame on a double-blind, placebo-controlled basis—that is to say, when neither they nor the administering physician knew whether they were receiving aspartame or a placebo—in that study, no correlation was found between aspartame consumption and headaches. Now, these are among people who sincerely believed, and based on their experience thought they were justified in believing, that aspartame was causing their headaches.

With your permission, Senator, I would like to submit a copy of that article for the record today.

Senator **Metzenbaum**. Who did the research on that?

Mr. **Shapiro**. Let me get the entire list. The article is headed "Aspartame and Susceptibility to Headache," and the investigators are Susan Schiffman, Ph.D.; C. Edward Buckley, M.D.; H.A. Sampson, M.D.; E.W. Massey, M.D.; J.N. Baraniuk, M.D.; J.V. Follett, M.D., and Z.S. Warwick, B.S.

Senator **Metzenbaum**. Was that an NIH or Government-financed investigation?

Mr. **Shapiro**. No, Senator. That was a study which the NutraSweet Company provided funds for upon the recommendation of the Centers for Disease Control and with the concurrence of the Food and Drug Administration, who reviewed the protocol for this study with us.

Senator **Metzenbaum**. What was the amount of the research grant?

Mr. **Shapiro**. I do not know the answer to that question, Senator, but I would be happy to submit it for the record.

Senator **Metzenbaum**. But that was financed entirely by NutraSweet?

Mr. **Shapiro**. Yes, Senator, I believe so. But I would like to verify that by looking in the publication.

Senator **Metzenbaum**. In the article's publication, will that be indicated in the publication, that it was financed by NutraSweet?

Mr. **Shapiro**. Yes. It states in the footnote on the first page of it: "Supported by a Grant RR-30 from the General Clinical Research Center's Program, Division of Research Resources, National Institutes of Health, and by a grant from the NutraSweet Company." So apparently, they had NIH funding in support as well as NutraSweet Company support.

Senator **Metzenbaum**. Thank you.

[The article referred to follows:]

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ASPARTAME AND SUSCEPTIBILITY TO HEADACHE

Susan S. Schiffman, Ph.D., C. Edward Buckley III, M.D., H.A. Sampson, M.D., E.W. Massey, M.D.,
J.N. Baraniuk, M.D., J.V. Follett, M.D., and Z.S. Warwick, B.S.

Abstract We performed a double-blind crossover trial of challenges with 30 mg of aspartame per kilogram of body weight or placebo in 40 subjects who reported having headaches repeatedly after consuming products containing aspartame. The incidence rate of headache after aspartame (35 percent) was not significantly different from that after placebo (45 percent) ($P<0.50$). No serious reactions were observed, and the incidence of symptoms other than headache following aspartame was also equivalent to that after placebo. No treatment-related effects were detected in vital signs, blood pressure, or plasma concentrations of cortisol, insulin, glucagon, histamine, epinephrine, or norepinephrine. Most of the subjects were well educated and overweight and had a family or personal history of allergic reactions. The subjects who had headaches had lower plasma concentrations of norepinephrine ($P<0.0002$) and epinephrine ($P<0.02$) just before the development of headache.

We conclude that in this population, aspartame is no more likely to produce headache than placebo. (N Engl J Med 1987; 317:1181-5.)

ASPARTAME is a dipeptide sweetener (L-aspartyl-L-phenylalanine methyl ester[1,2]) that is 180 to 200 times sweeter by weight than sugar. The Food and Drug Administration approved the use of aspartame as a table-top sweetener and an ingredient in dry foods in 1981[3] and approved its use in carbonated beverages in 1983.[4] The widespread use of aspartame provoked reports of various reactions attributed to sensitivity to the sweetener.[5-7] The Centers for Disease Control (CDC) investigated 517 consumer complaints and found that 67 percent involved neurologic or behavioral symptoms, especially headaches.[6,7] Other case reports of adverse reactions to the sweetener have included migraine,[8] granulomatous panniculitis,[9] and urticaria.[10] Experimental studies in rats and mice[11,12] have indicated that the phenylalanine in aspartame may alter brain concentrations of bioamines, and it has been suggested that similar changes may cause the neurologic symptoms reported in humans.[13,14]

The studies by the CDC[6,7] have suggested that a well-designed clinical trial focused on a specific symptom in susceptible subjects might determine whether or not aspartame causes the symptom. This report describes the outcome of a double-blind study of 40 subjects who had reported repeated headaches following the ingestion of products containing aspartame.

METHODS

Subject Selection

The 40 subjects selected for this study had a history of headache and related neurologic symptoms within 24 hours after consuming products containing aspartame. The subjects were identified by their prior complaints to G.D. Searle and Company (the Nutra-Sweet Company), manufacturers of products containing aspartame, or to the FDA. The criteria for selecting subjects were consistent with the guidelines for establishing a possible cause-and-effect relation between aspartame ingestion and symptoms that had been set down by the CDC.[6,7] Specifically, each subject had either headaches following the ingestion of several products containing aspartame, or repeated headaches after ingesting a single aspartame-containing product after a period of abstinence from that product.

The sample size of 40 subjects was chosen because it is sufficient to ensure that a difference of 33 percent in the incidence rates of headache during the two treatments could be detected by a test done at the 5 percent significance level, with an approximate power of 0.90.[15] All 40 participants were free of major medical problems. Persons who were using medications (e.g., antihistamines or beta-blockers) that might have interfered with the experimental studies were excluded. All subjects were at least 18 years of age and provided written informed consent before participating in the study. In addition, they refrained from ingesting products containing aspartame for at least 48 hours before entry into the study.

Clinical Studies and Description of Subjects

A medical history was taken, and a physical examination, electrocardiography, consultative neurologic evaluation, and electroencephalography were performed during the first two days of hospitalization. The medical history included a listing of the subjects' use of all over-the-counter, prescription, and street drugs and of alcohol, caffeine, and tobacco. The headache history included the location, intensity, frequency, and duration of headache, associated symptoms, and mechanisms of relief. Chest radiography was done only in the subjects who presented with a history of recent lower respiratory tract symptoms. On the first day of the hospitalization, an indwelling catheter with a heparin lock was placed in a peripheral arm vein and used to obtain the initial blood samples and experimental samples on subsequent study days. Serum levels of β-subunit human chorionic gonadotropin were measured in all fertile women to exclude pregnancy. The clinical laboratory studies for each subject included a complete blood count, a differential count and examination of the stained blood film, urinalysis, and blood-chemistry studies (measuring calcium, phosphorus, creatinine, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, lactic dehydrogenase, aspartate and alanine aminotransferases, sodium, potassium, chloride, bicarbonate, glucose, and blood urea nitrogen). After completion of the experimental challenges, percutaneous tests were done with 115 conventional allergens (pollens, inhalants, and molds) and appropriate saline, histamine (15 to 120 mM), and methacholine (80 to 640 mM) controls. The reactions to the controls were analyzed by methods described previously, to obtain estimates of responsiveness and sensitivity to histamine and methacholine.[16]

The clinical and laboratory findings in the 41 candidates for the study were reviewed before their inclusion. On questioning by a neurologist (E.W.M.), all were found to have characteristic vascular headaches. Most of the subjects had had headaches before using aspartame, and all had a history of vascular headaches that they associated with the use of products containing aspartame. One person was excluded because of a history of seizures, and the remaining 40 subjects completed the study. One of the 40 had a history of stroke, with subsequent recovery of motor and sensory function.

From the Departments of Psychiatry, Medicine, and Pediatrics, Duke University, Durham, N.C. Address reprint requests to Dr. Schiffman at the Department of Psychiatry, Duke University Medical Center, Durham, NC 27710.

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Neurologic evaluation revealed residual right-sided weakness, and computerized tomography of the brain revealed changes consistent with an old parietal-lobe infarct. This person was studied. The demographic and physical characteristics of the 40 subjects accepted for study are shown in Table 1. The subjects' residences were widely distributed across the United States, in 25 of the 50 states. Subjects included the vice presidents of a bank and a media service, computer data-processing managers, a business office administrator, a business statistician, an executive recruiter, a certified public accountant, several executive-level administrative assistants or secretaries, a graphics designer, a sales director, several salespersons, a professional pianist, several social service counselors, a college professor, a college instructor in education, a high-school teacher, a physician, a research assistant, several nurses, a medical secretary, a machinist, a waitress, a grocery clerk, a medical student, and college students. Two subjects were homemakers; another was retired, and one was unemployed.

In relation to current standards,[17] 22 subjects (55 percent) were more than 10 percent overweight, 12 (30 percent) were more than 25 percent overweight, and 6 (15 percent) were more than 50 percent overweight. The history of exposure to aspartame revealed that 25 subjects identified two or more categories of products that prompted their complaints. Seventy-four product categories were mentioned, including carbonated soft drinks (49 percent), noncarbonated drinks (14 percent), table-top sweeteners (14 percent), and other products containing aspartame (23 percent). Seven subjects smoked cigarettes. Two subjects had a history and physical findings consistent with mitral-valve prolapse. The sample included 20 subjects (50 percent) with a history of previous surgery requiring general anesthesia. Fourteen subjects (35 percent) had undergone clinical evaluation of headache. Twenty-three (57 percent) had a personal or family history of allergic rhinitis, asthma, or urticaria. Sixteen subjects (40 percent) reported a history of reaction to drugs or radiocontrast mediums. Collectively, 28 (70 percent) had a personal or family history of one or another type of allergic reactivity.

Study Design

The experimental design and plan for the double-blind crossover study (Table 2) were approved by the institutional review board and the research committee of the Duke University Medical Center Research Unit, where each subject was studied as an inpatient. The research-unit dietician obtained a dietary history from each subject and, on the basis of his or her eating habits, drew up a menu for each subject that was equivalent in calories and nutritional composition for the days before each challenge and for each challenge day. The subjects received breakfast, lunch, and dinner daily at 8 a.m., 12 p.m., and 6 p.m., respectively. The blinded challenges were conducted on the third and fifth hospital days, with an interposed "washout" day. On each study day, the subject was given either aspartame or placebo, according to a randomized, double-blind, crossover design. The test articles were delivered in capsule form, so that aspartame could not be distinguished from placebo on the basis of taste. Sequential challenges with 10 mg of aspartame per kilogram of body weight were administered at 8 a.m., 10 a.m., and 12 noon. In an adult weighing 70 kg, this total dose of 30 mg per kilogram is equivalent to the quantity of aspartame in approximately 4 liters of a carbonated soft drink. The aspartame lot used (no. RLT-7567) was analyzed and found to be 98 percent pure aspartame (α-aspartyl-phenylalanine methyl ester). Other components included 0.17 percent α-aspartyl-phenylalanine, 0.56 percent aspartyl phenylalanine diketopiperazine, 0.32 percent β-aspartyl-phenylalanine methyl ester, and small quantities of other conversion products, such as β-aspartyl-phenylalanine and phenylalanine methyl ester. The placebo consisted of identical capsules containing microcrystalline cellulose.

Table 1. Demographic and Physical Characteristics of 40 Subjects Challenged with Aspartame.

Characteristic	
	no. (%)
Sex	
Male	12 (30.0)
Female	28 (70.0)
Race or ethnic origin	
White	36 (90.0)
Black	1 (2.5)
Asian	2 (5.0)
Hispanic	1 (2.5)
	mean ±SEM
Age (yr) (range, 18.8–68.9)	33.5±1.90
Height (cm)	166.8±1.37
Weight (kg)	76.9±3.49
Temperature (°C)	36.7±0.08
Pulse (per minute)	80.1±1.99
Respirations (per minute)	19.1±0.40
Blood pressure (mm Hg)	
Systolic	118.4±2.49
Diastolic	74.8±1.92

Each subject was closely monitored during the experimental challenges. The severity of headaches and related symptoms was evaluated independently by the subject and the study investigator when they occurred. Retrospective assessments of the symptoms were recorded by the research-ward staff in the form of progress notes. To indicate the severity of the headache, the subject placed an x along a line that was coded from 0 for "absent" to 100 for "intolerable" headache. The investigator evaluated the severity of the headache as "mild," "moderate," or "severe" and described the occurrence of other associated symptoms. Screening studies of potentially relevant blood-chemistry indexes were done on the second day of hospitalization before the experimental studies and at 7:45 a.m., 9 a.m., 11 a.m., and 4 p.m. on the two study days. These studies included measurements (Table 2) of cortisol (competitive protein binding), insulin (radioimmunoassay, double-antibody method), glucagon (radioimmunoassay), glucose, histamine (single radioenzymatic assay using purified histamine methyl transferase), epinephrine (high-performance liquid chromatography), and norepinephrine (high-performance liquid chromatography).[18-22] Similar blood-chemistry studies were performed at the onset of each subject's awareness of headache or other important symptoms during the course of the experimental challenge.

Analysis of Observations

The record of adverse clinical symptoms kept by each subject and the reports of symptoms to the investigator and the research-ward staff were evaluated for consistency among observers before the study was unblinded. This assessment revealed that the subjects had reported consistent information about headache and associated vascular symptoms to all observers. Before the study was unblinded, these symptoms were evaluated in relation to the screening values of glucose, insulin, glucagon, histamine, cortisol, epinephrine, and norepinephrine, and a relation between low plasma concentrations of norepinephrine and the subsequent development of headache was identified. After the study was unblinded, subjects were categorized according to the timing of adverse events, including headache, as follows: (1) on the day aspartame but not placebo was given; (2) on the day placebo but not aspartame was given; (3) on both treatment days; and (4) on neither day. The incidence of symptoms was analyzed by the exact form of McNemar's test.[15,23] Measured data were analyzed by the analysis of variance appropriate for a two-period, two-treatment crossover study. All P values reported for pairwise comparisons were two-tailed.

RESULTS

The incidences of adverse events on days of aspartame and placebo treatment are shown in Table 3. Twenty-six of the 40 subjects reported headache during the experimental study and identified one or more

Table 2. Study Schedule.

Day	Study Procedure	Laboratory Test*	Times
1	Medical history and physical examination	EEG, EKG (all subjects had a normal EEG and EKG)	
2		Routine hematologic studies Routine blood-chemistry studies Urinalysis Base-line vital signs Base-line blood-chemistry studies (glucose, glucagon, insulin, epinephrine, norepinephrine, histamine, cortisol)	
3	First challenge day	Base-line and treatment blood-chemistry studies (glucose, glucagon, insulin, epinephrine, norepinephrine, histamine, cortisol) Vital signs	7:45 a.m., 9 a.m., 11 a.m., 4 p.m. (and at the time of any adverse event)
	Administration of aspartame or placebo		8 a.m., 10 a.m., 12 noon
4	Washout from day 3		
5	Second challenge day and crossover from day 3	Same as day 3	Same as day 3
6		Allergy testing	

*EEG denotes electroencephalography, and EKG electrocardiography.

days on which they thought they might have received aspartame. Despite this perception, only eight subjects considered their post-challenge symptoms identical to those previously attributed to the ingestion of products containing aspartame. The headaches were mild to moderate in intensity and not associated with focal neurologic findings. Eight subjects had headache while receiving aspartame but not placebo. Twelve subjects had headache while receiving placebo but not aspartame. Six subjects had headache during both treatments. When these six subjects were included, the incidence of headache was 35 percent with aspartame and 45 percent with placebo. The incidence of adverse symptoms with placebo was equivalent to that with aspartame (Table 3). In addition, differences in the severity, time of onset, and duration of headache with placebo were equivalent to those with aspartame (Table 4). Furthermore, an analysis of the concentrations of glucose, insulin, glucagon, histamine, cortisol, epinephrine, and norepinephrine in all 40 subjects revealed no abnormal values. Evaluation of all 40 subjects revealed only one treatment-related difference (the glucose level in the treatment group was lower eight hours after the start of the challenge). Although this difference is interesting, it must be interpreted with caution. Statistically significant comparisons would be expected 5 percent of the time by chance in comparisons of random observations.[23]

These negative findings prompted additional assessments of possible relations between the pulse rate, blood pressure, and plasma biochemical factors and the occurrence of headache. Observations made on days when a headache occurred, independently of treatment, were separated from observations made on headache-free days. The observations on the day of headache were further divided into those made before and those made during the headache. On the days on which a headache occurred, the plasma norepinephrine concentration was 251.2 pg per milliliter before headache (Table 5), and there was a statistically significant increase to 349.4 pg per milliliter in the same subjects during headache ($P<0.0002$). The plasma epinephrine concentration was 18.7 pg per milliliter before headache, and there was a significant increase to 25.6 pg per milliliter during headache ($P<0.02$). During headache, the mean plasma concentrations of norepinephrine and epinephrine were equivalent to those observed on headache-free days. The increases in catecholamines appear to be functionally important, because pulse pressure was significantly higher during headache than before it ($P<0.01$).

The subject's reactivity to skin-test allergens was compared with the results of similar tests in 54 patients with active allergic symptoms and a representative sample of the U.S. population.[24] As a group, the 40 subjects were intermediate in reactivity between the national sample and the 54 patients with active allergic disease. The interesting relation between headache and changes in plasma norepinephrine level prompted an evaluation of how these trends related to allergy and body weight. During the experimental studies, subjects with a personal or family history of allergy had a mean (±SEM) screening norepinephrine level of 251.4±26.8 pg per milliliter, whereas the subjects with no such history of allergy averaged 359.9±57.2 pg per milliliter ($P<0.06$). Surprisingly, the average base-line norepinephrine level in subjects

Table 3. Numbers of Subjects with Adverse Symptoms According to Treatment.*

Symptom	Aspartame	Placebo	Both	Neither
Headache	8	12	6	14
Dizziness	3	3	1	33
Fatigue	3	3	0	34
Nausea	4	5	0	31
Numbness	0	1	0	39
Tinnitus	1	1	0	38
Visual impairment	2	1	2	35
Anxiety	3	2	0	35
Disorientation	1	1	0	38
Other symptoms	8	12	6	14
Any symptom except headache	11	13	8	8

*Headache occurred with both treatments, neither treatment, aspartame and not placebo, and placebo and not aspartame. P values for McNemar's test in the exact form ranged from 0.50 for headache to 1.00 for the symptoms that occurred less frequently. The 95 percent confidence interval for the difference in incidence rates between aspartame and placebo was −35 to +12 percent.

Table 4. Mean (±SEM) Characteristics of Headache According to Treatment.

	ASPARTAME	PLACEBO	P VALUE
Severity			
Investigator*	1.4±0.13	1.2±0.10	0.42
Patient (analogue scale)	41.0±7.05	40.5±5.78	0.95
Onset of headache (no. of hours after 8 a.m.)	5.7±1.79	4.7±1.28	0.64
Duration of headaches (no. of hours)	6.2±1.71	4.3±1.17	0.36

*A score of 1 denotes mild, 2 moderate, and 3 severe.

with more than 10 percent excess body weight was 235.7±35.3 pg per milliliter, and that in the remaining subjects was 347.8±36.4 (P<0.034).

DISCUSSION

The administration over a period of four hours of 30 mg of aspartame per kilogram of body weight in three encapsulated doses of 10 mg per kilogram each elicited an incidence of headache comparable to that elicited by placebo in this randomized, double-blind, crossover study. This finding was unexpected, because each subject had previously attributed his or her headaches to consumption of products containing aspartame. This experimental approach and outcome differ from those of the single-case study of aspartame challenge by Johns,[8] who gave the subject solutions of aspartame, saccharin, and sucrose, which can be distinguished from one another by taste or viscosity at the concentrations used.

Although the headaches detected in this study did not occur more frequently after aspartame than after placebo, several interesting findings did emerge. First, when the occurrence of headache was evaluated independently of treatment, the plasma norepinephrine and epinephrine levels were significantly lower before headache and exhibited a statistically significant increase during the period of headache to concentrations equivalent to those in subjects who did not have headache. This observation is consistent with the findings of Gotoh et al.,[25] who noted significantly lower levels of plasma norepinephrine in patients with migraine who were studied during headache-free intervals. Irrespective of the presence or absence of headache, no significant differences were detected in the circulating concentrations of norepinephrine at any time in subjects receiving aspartame as compared with placebo. This observation is interesting in that aspartame is a source of phenylalanine, and increases in plasma phenylalanine and tyrosine have been reported after the ingestion of large doses of aspartame.[26,27] Biogenic amines, such as norepinephrine, can be derived from tyrosine. Norepinephrine and other biogenic amines have been implicated in the pathogenesis of vascular headaches.[28-30]

Table 5. A Comparison of Norepinephrine and Epinephrine Levels and of Pulse Pressure on Study Days without Headache and before and during Headache.*

	WITHOUT HEADACHE	WITH HEADACHE		
		BEFORE	DURING	P VALUE
Norepinephrine (pg/ml)				
Mean	329.8	251.2	349.4	<0.0002
SEM	20.4	32.1	32.6	
Epinephrine (pg/ml)				
Mean	25.1	18.7	25.6	<0.02
SEM	2.1	2.1	2.8	
Pulse pressure (mm Hg)				
Mean	40.2	38.3	43.5	<0.01
SEM	1.1	1.3	2.0	

*P values in table compare norepinephrine, epinephrine, and pulse pressure before and during headache. The differences between norepinephrine and epinephrine concentrations in subjects on study days without headache and on study days before headache were also significant (P<0.04 for both). Differences between observations on study days during headache and study days without headache were small and not significant (P<0.13 or more).

The large number of overweight, well-educated subjects with personal or family histories of allergic reactions in this sample may not be the result of chance. First, persons with excess body weight are likely to have sampled products containing aspartame. Second, patients with known allergies are generally more highly educated[24] and aware of exposure-related symptoms. Their heightened awareness of potential allergic substances is adaptive in that it leads to identification and avoidance of novel sources of exposure. The behavior of such people contributes to public opinion about products in their communities. Finally, the low-normal norepinephrine levels observed in our subjects before headache are not inconsistent with the heightened α-adrenergic reactivity characteristic of allergic patients with active disease.[31]

In conclusion, the incidence of headache after short-term challenge with 30 mg of aspartame per kilogram was equivalent to that after placebo. This finding emphasizes the importance of double-blind studies to assess adverse reactions to a food or food ingredients.[32-34]

We are indebted to Ms. K. Abelkop and Ms. L. Veasey for their assistance with the double-blind challenges, and to Mrs. Nita Packer for preparation of the manuscript.

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Mr. **Shapiro.** Obviously, Senator, no one in this room or anywhere in this country can fail to sympathize with people who are ill, with people who suffer seizures, headaches, or any other form of human ailment. But sympathy with their condition ought not be translated into an attribution of that condition to a particular cause such as aspartame consumption, when in fact that attribution has no support in the scientific record.

The fact is that each year 100,000 people in this country will have seizures for the first time in their lives; about half of those people, if they are typical of the population as a whole, will be regular consumers of products containing NutraSweet. That is 50,000 first-time seizures. Nothing could be more unfair or, I would submit, tragic, than for those people to believe that their seizures have been caused by aspartame when such has not been shown to be the fact.

The risk involved in people making misdiagnoses and misattributions of their conditions is a grave one and one which I certainly view with concern.

With respect to the two witnesses you have heard today who believe they have had seizures as a result of aspartame consumption, I would invite them to participate in the ongoing double-blind, placebo-controlled studies taking place at universities in the United States, in order to determine whether or not aspartame is the cause of their conditions. And I would make the same invitation to those patients of Dr. Miller who believe their headaches are caused by aspartame.

The third theme of the testimony you have heard today rests on the theories of some scientists—and they were well-represented today—as to the effects of the essential amino acid phenylalanine which is, as you know, a constituent of aspartame and of virtually all protein in the diet.

Here I want to point out only, without entering into a debate which I am not qualified to participate in, that the views of these witnesses are well-known to and well-understood by the Food and Drug Administration and by the other regulatory agencies of the world. On those occasions in the past when those views have been advanced and have been reviewed and considered by the FDA and other agencies, they have been rejected on their scientific merits.

One particular point which kept coming up in your discussion with the scientific panel had to do with consumption levels of aspartame. And there was a great deal of speculation as to what a five-year-old might consume or might not consume. The fact is there is no need to speculate on that subject, Senator. Those data are regularly collected, provided to the FDA under the authority of the FDA and I believe are contained in Commissioner Young's written testimony. If they are not, I would be happy to supply those data for the record. What they do show is that even in the case of the highest consumers among the youngest elements of the population, the consumption of aspartame nowhere approaches the levels suggested by some of the witnesses today.

Finally, Senator, I am left, at the conclusion of all the testimony you have heard today with some concern lest the public observing these hearings be left with a sense of confusion.

Different witnesses have said contradictory things. Since most of us are not competent to make decisions as to which scientists are right and which scientists are wrong, how, then, are we as a matter of public policy, how, then, are we as individual consumers to make the decisions that we have to make in order to get on with our lives?

I believe there is an answer to that question, and I believe it is the answer which Congress has provided and which indeed the legislative authorities of every other advanced nation of the world have provided. You have created an independent expert scientific agency, the Food and Drug Administration, and you have periodically strengthened its authority when you have thought that to be lacking, or improved its procedures when you have thought them to be inadequate. You fund them, and you fund them extensively. And you do all that for one reason and one reason only—to undertake independent, unbiased, expert reviews of scientific evidence and based on the evidence authoritatively to resolve issues of this nature. That is a grave responsibility you have entrusted to them, the responsibility of determining on the basis of the science what may and what may not be permitted in our food supply to be consumed by our people.

It is noteworthy that every other industrial society in the world has done exactly the same thing and for exactly the same reason. The reason is it is the best way—indeed, it is the only sane and valid way—to resolve issues such as those we have been discussing today.

When questions of science arise with respect to food safety, the Congress and the public are entitled to an authoritative resolution of those questions. You have given that task to the FDA. In the case of aspartame, the FDA has provided you and the public with the answer: Aspartame is safe. It is unanimously supported in that conclusion by the independent agencies who carry the same grave responsibilities in their respective nations.

The issue of aspartame safety, Senator, can be debated only so long as one ignores the authoritative conclusions of the agencies that are responsible for deciding that issue. The questions have been asked and answered, not once but repeatedly, not only here but around the world. To continue to ask the questions and to ignore the answers is an unjustifiable disservice to the public, sir.

Thank you.

[The prepared statement of Mr. Shapiro follows:]

Statement of
Robert B. Shapiro
Chairman of the Board and
Chief Executive Officer
The NutraSweet Company
before the
Committee on Labor and Human Resources
United States Senate
November 3, 1987

Mr. Chairman, members of the Committee, I am Robert Shapiro, Chairman and Chief Executive Officer of The NutraSweet Company. The NutraSweet Company manufactures and markets the sweetener aspartame under the brand name NutraSweet and also markets the tabletop sugar substitute, Equal, which contains NutraSweet. I am pleased to appear at this hearing to assist the Committee.

My testimony today will address three main topics:

> First, the nature of aspartame, its role in wholesome and nutritious diets and its safety. Let me state at the outset: aspartame is safe and its safety has been repeatedly, definitively and conclusively demonstrated.
>
> Second, the nature of the so-called controversy about aspartame safety that some of today's witnesses have for years sought to generate. Their views have been considered and rejected by the scientific and regulatory community around the world and by the courts.

Third, I will suggest that there exists a well-established means for finally and authoritatively resolving issues of this nature. It is the scientific process, and it is properly applied to issues of food safety through the regulatory processes which have been established by the Congress and by legislative authorities in every industrial society around the world. That process has been exhaustively applied to the issues that have once again been aired today, and its results are clear and dispositive of those issues.

1. Aspartame. NutraSweet brand sweetener has become a regular and routine part of the diets of approximately 200 million people around the world. It has been consumed on literally billions and billions of occasions by hundreds of millions of people representing the full range of human diversity. The reaason it is so widely used is simply that it plays a useful role in people's lives.

Its benefits are clear:

- It tastes good.
- It is low in calories
- It does not promote cavities.
- It is safe.

Because NutraSweet is all of these things, it helps people deal with health problems which are universally recognized as serious in industrial societies around the world: obesity and its associated medical problems, dental caries and balanced nutrition. It is, of course, a blessing to tens of millions of diabetics.

The Supreme Court of Victoria (Australia) recently granted a ten-year patent extension for aspartame, holding that it "clearly" is an invention of more than ordinary utility "in terms of public health." And millions of people use NutraSweet simply because it fits well in the active, fit and healthy lifestyles that people around the world are increasingly adopting.

Obviously, however, the value of those benefits would be largely or entirely offset if aspartame were not safe for consumption by this very large and diverse population -- a population that includes children, older people, pregnant women, diabetics, and people who have all the diversity of genetics, environment and personal health that constitute the general population. Because that is so obviously true, regulatory authorities throughout the world have quite properly insisted on full scrutiny and review of the scientific record before allowing aspartame to be introduced into the food supply of their countries.

In the United States, aspartame is the only sweetener in history that was subjected to the full regulatory review, scrutiny and approval of the Food and Drug Administration as provided by the Congress in the 1958 amendments to the Food, Drug and Cosmetic Act. All previous sweeteners, such as saccharin and cyclamate, entered the food supply long before the 1958 amendments. As a result, aspartame is the only sweetener that was subjected to comprehensive animal and human testing prior to its introduction.

As you have heard today, the three components of aspartame are all well-known and familiar constituents of foods that the human race has been ingesting since the very origins of people and food. Not surprisingly, these components of aspartame have been shown to be treated by the body exactly as they are treated when they are ingested in milk, meat, fruit, vegetables and other familiar sources.

Aspartame has been tested in every applicable species, including man. We know, and the FDA knows, and the worldwide scientific and regulatory community knows its pharmacology, its metabolism and its lack of adverse effects in humans, and such sub-groups of the population as diabetics, obese individuals, children, and even in-individuals with the genetic defect known as phenylketonuria. These things are known because they have been studied in accordance with well-established scientific method.

After carefully reviewing the unprecedented mass of data which came out of these detailed studies, the worldwide regulatory and scientific community has been unanimous in its praise for the thoroughness of the scientific record -- and unanimous also in its conclusion that aspartame is safe.

The Commissioner of the FDA in 1981 stated: "Few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety."

The Canadian Health Protection Branch has declared: "In so far as the data submitted in support of the safety of aspartame is concerned, it can be stated that the substance is one of the most extensively studied chemicals permitted for use in food." And, "The data on the safety of aspartame are the most comprehensive ever received by the Health Protection Branch in support of a food additive." Finally, the HPB concluded that "aspartame would not pose any hazard to health" when used as approved.

The Danish Food Institute, in May of this year, following a thorough reappraisal of the data -- a reappraisal which was occasioned by the same kinds of allegations you have heard today -- reaffirmed its previous conclusion that aspartame is safe, saying: "It is quite certain that research published in the scientific literature and/or studied in detail by governments and independent scientific committees maintains that the use of aspartame as an additive does not bear any health risk at all."

The Council on Scientific Affairs of the American Medical Association reported in its review of aspartame safety research: "Consumption of aspartame by normal humans is safe and not associated with serious, adverse health effects."

These are but a few of the many independent scientific organizations and regulatory authorities who have reviewed all the data -- including the various allegations that have been repeated here today -- and have concluded that aspartame is safe. The Joint Expert Committee on Food Additives of the World Health Organization, the Scientific Committee on Foods of the European Common Market, The American Diabetes Association, the Epilepsy Institute, The American Academy of Pediatrics, and the regulatory agencies of more than 60 countries around the world have unanimously and without exception determined that aspartame is safe.

Nor can it be suggested that these are agencies that are slack or promiscuous in approving sweeteners. To date, the FDA has never approved an intense sweetener other than aspartame. It was the FDA, you will recall, that banned cyclamate and sought to ban saccharin (in the latter case, its ban has been stayed by the Congress). In Canada, aspartame is the only low-calorie sweetener allowed to sweeten foods and beverages; and aspartame is the only intense sweetener ever to be approved in Japan.

The fact is that all advanced nations have established careful, cautious scientific and regulatory processes to assure the safety of their food supply. All have independently reviewed the scientific data on aspartame; all have affirmed its safety.

What is remarkable about aspartame is not controversy; rather, it is the unanimity and uniformity of the worldwide scientific consensus as to its safety.

2. The "Controversy." In the face of the documented and unequivocal unanimity of the world scientific and regulatory community, why has this Committee heard testimony today which seeks to create an impression of scientific controversy on aspartame safety?

The testimony repeats once again in this public forum three themes that have been repeatedly considered and found to be without merit over the years.

The first theme consists of criticisms of the FDA approval process, either in general or in the specific case of aspartame. These criticisms are demonstrably groundless:

The FDA's process in approving aspartame has been exhaustively reviewed by the General Accounting Office at Senator Metzenbaum's request. The integrity and propriety of that process was fully vindicated.

The FDA's approval of aspartame was also reviewed by the United States Court of Appeals for the District of Columbia in a lawsuit brought by James Turner and the Community Nutrition Institute. In a unanimous opinion, written by Judge Abner Mikva, the approval was sustained.

Finally, criticisms of the FDA approval process must also be understood as criticisms of the approval processes of all the other nations of the world which have independently reviewed the same data and come to the same conclusions as the FDA. If something is wrong at the FDA, the same thing must be wrong in Canada, England, Germany, Switzerland, Japan, France, the Scandinavian countries, the World Health Organization, and all the rest.

The second theme of the testimony you have heard rests on anecdotal complaint.

Hundreds of millions of people consume products sweetened with aspartame. It is absolutely inevitable that every day a certain percentage of those people will suffer all the ailments of every sort that afflict humanity. A few of these people, such as those you heard today, assert that their ailments are caused by aspartame consumption.

It is, or should be, obvious that a relationship in time between two events in itself says nothing about causation. As Dr. Arthur Raines, Professor and Acting Chairman of the Department of Pharmacology at Georgetown University, recently wrote in a letter to the Washington Post:

> "As aspartame is estimated to be consumed by about half the U.S. population, one need not be a epidemiologist to grasp

> the problem of establishing any cause-and-effect relationship. Half the headaches in America would be expected to occur in aspartame users, as would half the seizures and half the purchases of Chevrolets."

There are only two ways of seeking to determine whether a cause-and-effect relationship exists. The first is epidemiological, in which large populations are analyzed to see if there is a statistically significant pattern correlating the alleged cause and the effect. The second is to do controlled clinical studies, in which people who have suffered some ill effect are exposed to the alleged cause on a double-blind basis (i.e., neither they nor the person conducting the study knows whether a particular exposure is to the alleged cause or to a placebo).

Both approaches have been used in the case of aspartame.

At the request of the FDA, the Centers for Disease Control evaluated 517 cases of people who believed aspartame had caused a symptom. In reporting its results, the CDC concluded:

> "Using the approach outlined, we were unable to identify a specific constellation of symptoms clearly related to aspartame consumption that would suggest a widespread public health hazard associated with aspartame use. Despite the great variety overall, most of the frequently reported symptoms were mild and are common in the general population. Some reports are undoubtedly due to the temporal coincidence of these symptoms with aspartame consumption, and other reports may be due to the suggestibility of some persons. However, some reports may be attributable to an as yet undefined sensitivity of some

individuals to aspartame in commonly-consumed amounts. Only focused clinical studies can thoroughly evaluate whether these cases were actually due to aspartame sensitivity."

It should be noted that many clinical studies had previously been conducted in humans without any indication of "sensitivity" or ill effect. It should also be noted that "sensitivity," should it exist, would be neither unusual in foods nor alarming: many individuals are sensitive to common foods, such as milk, strawberries or seafood.

Nonetheless, in order to determine whether any ill effects were in fact attributable to aspartame "sensitivity," in cooperation with the FDA, we awarded grants to several independent university research centers to conduct focused clinical studies with subjects who believed aspartame had caused their symptoms. The results of these studies will be published in peer-reviewed academic journals as they are completed.

The Committee may be interested in knowing that the results of one such study, involving people who believed their headaches were caused by aspartame, will be published later this week in the New England Journal of Medicine. The results should be of interest to those who seek in good faith to evaluate the significance of these anecdotal complaints.

The FDA continues to study, analyze and monitor all allegations of aspartame causing ill effects. The FDA's published conclusions are identical to those of the CDC and support no causal relationship to aspartame consumption.

No one can fail to sympathize with people who are ill. But sympathy with their condition should not be translated into an attribution of that condition to aspartame consumption. Such an attribution has no support in the scientific record.

Indeed, I must express grave concern at the harm that these unsubstantiated allegations can cause, not only to the millions of people who use aspartame and are entitled to continue to use it without anxiety, but even more importantly to people who may falsely believe that a particular symptom is caused by aspartame and thus fail to get proper medical diagnosis and treatment for the actual cause of their symptoms.

The third theme of the testimony you have heard rests on the theories of some scientists as to the effects of the essential amino acid phenylalanine, a constituent of aspartame and of virtually all protein in the diet. Others have already explained why such theories are not widely accepted in the scientific community. I will point out only that the views of the witnesses you have heard today are well-known to, and well-understood by the FDA and the other regulatory agencies around the world. On each occasion when those views have been reviewed and considered, they have been explicitly rejected on the scientific merits.

3. Resolving the Issues. Any non-scientist who has attended today's hearing may feel a justifiable sense of confusion. Different witnesses have said contradictory things: since non-scientists cannot competently make scientific judgements, whom are we to believe?

There is an answer to that question, one which the Congress has recognized since the turn of the century. You need not and ought not rely on the assertions of manufacturers, on anecdotal complaints, on newspaper reports or on the views of individual scientists.

Congress, by law, has created the mechanism by which the issues of what is safe, and not safe, in our food supply can be scientifically examined and scientifically resolved. You have created, you have periodically strengthened, and you continue to fund the Food and Drug Administration for one purpose only: to undertake independent, expert reviews of the scientific evidence and, based on the evidence, authoritatively to resolve issues of this nature.

You have entrusted them with the grave responsibility of determining on the basis of scientific evidence what may, and what may not, be permitted in our food supply. It is noteworthy that every other industrial society in the world has done the same thing, and for the same reason: it is the best way -- indeed, it is the only sane and valid way -- to resolve issues such as those we have been discussing today.

The FDA and comparable agencies throughout the world take that responsibility very seriously. They are expert, they are thorough and they are extremely cautious, as their record demonstrates.

It is, I think, both untrue and insulting to suggest that the FDA, and the similar agencies around the world, are somehow less concerned about food safety, or less competent, than those who, without that responsibility, would criticize their findings.

When questions of science arise with respect to food safety, the Congress and the public are entitled to an authoritative resolution of those questions. You have given that task to the FDA. In the case of aspartame, the FDA has provided you and the public with the answer: Aspartame is safe.

It is unanimously supported in that conclusion by the independent agencies who carry the same responsibilities in their respective nations.

The issue of aspartame safety can be debated only so long as one ignores the authoritative conclusions of the agencies that are responsible for deciding that issue. The questions have been asked and answered -- not once but repeatedly, not only here but around the world. To continue to ask the questions and ignore the answers is an unjustifiable disservice to the public.

Senator **Metzenbaum**. I think each of us has to make that determination in his or her own mind, Mr. Shapiro.

How do you account for testimony of Dr. Verrett, who tells us that the original study was so flawed that she raised the question and was quieted down, and then the letter from a man in your company saying get everybody in a frame of mind to say yes, yes, yes? Don't things like that bother you?

Mr. **Shapiro**. Well, first of all, I did not understand Dr. Verrett to say anything about a letter from anybody in our company. That was a question you had asked——

Senator **Metzenbaum**. No, no. That is correct. Dr. Verrett did not.

Mr. **Shapiro**. Dr. Verrett's critique of the scientific evidence is well-known to and has been considered by the Food and Drug Administration, which went through elaborate and in many respects unique processes to assure itself that the data on which it was basing its approval were data upon which it could rely. Those processes took years and years. You have heard the Commissioner today say he is satisfied with those processes. The regulatory authorities of other nations around the world are satisfied with the data on which they are basing their conclusions.

Indeed, there is a great deal of additional data which has been generated since the time of those original studies, because we are talking here about a period of more than 20 years, and all that has led those people in the world who are competent to make judgments on this subject to one, single conclusion.

Senator **Metzenbaum**. Mr. Shapiro, how do you account for Dr. Wurtman, a very prominent clinician, in a very responsible position at MIT, Dr. Elsas, a very prominent physician in a position at Emory, Dr. Miller from San Antonio, Texas, and Dr. Pardridge, all being so concerned, no personal gain for them to be raising the alarm signals--does it not cause you some concern? Can they just make these things up?

Do you remember when Senator Russell Long spoke on the Floor of the Senate and told a similar anecdotal story about his daughter, who had been having continued headaches and problems, and the doctor one day asked her if she was using NutraSweet, and she said she was. He told her to stop it, and immediately her condition improved. Are all these things just like faith healers, so to speak?

Mr. **Shapiro**. No. I think you have in that question asked a number of separate questions. With respect to Senator Long, we were aware of that and asked him whether his daughter would like to participate in a study to determine whether in fact her headache was caused by aspartame, and Senator Long said she did not want to do that.

With respect to the scientists, it is the nature, it is the function, it is the purpose of scientists to ask every question they can think of to ask about a substance which is a) of scientific interest and b) of public health importance, such as this.

And I would not criticize or fault any of the scientific witnesses you have heard today for vociferously, vigorously expressing their views. But they have been doing that for some time, Senator, and their views, as I say, are quite well-known. They have been responded to by other scientists. They are studied and monitored and analyzed by the Food and Drug Administration, and thus far nothing they have said has caused either the FDA or any of the other agencies I have referred to to change their views with respect to the safety of aspartame.

Senator **Metzenbaum**. You just reported today about the study that is going to be published by the New England Journal of Medicine on headaches. I remember that study; I remember hearing about it a long time ago. I remember calling the person who headed it up, because I could not believe the information that had been supplied to me, that a person who was going to head up that study was a psychologist, a taste physiologist, not a medical doctor at all. And I have difficulty in understanding how would a company such as yours choose such a person, a physiologist, a psychologist, to head up a clinical study of that kind which was subsequently published in the Journal of the American Medical Association?

Mr. **Shapiro**. Senator, as I think I previously noted, the study team included five M.D.s. One of the reasons that Dr. Schiffman was involved was because she has extensive experience in the conduct of studies of this nature—studies in which food and food-related substances are administered to determine physiological or other effect. It is an area in which she is quite well-known. And what I think one needs to bear in mind in evaluating this study is that it is not the product of a single person; it is the product of a seven-person research team, five members of which are M.D.s.

Senator **Metzenbaum**. But it just seems to me a judgmental question with respect to Searle.

A UPI story on this subject stated the following: "Susan Schiffman, named to head a Searle-funded Duke University Medical School study into NutraSweet's link to headaches, is a former General Foods and Searle consultant. Her research at Duke, where the Medical School has a new Searle Center, has fallen under the office of University Vice President William Anlyon, a former Searle Director. Schiffman said Anlyon had no role in Searle's promise to cover all costs of the study, expected to cost 'hundreds of thousands of dollars'. She said she took no salary for her work."

Do you remember you and I had long discussions about trying to work out some agreement to fund some further studies in this area, and I had concerns about the kind of people who would be chosen for those studies. And you take a person who has been a former consultant to your company; she is associated at the Searle-funded Duke University Medical School, where there is a Searle Center. Whether or not there is any impropriety, it has all the appearances that she would have a bias in favor of protecting the interests of Searle.

Doesn't that make you think a bit?

Mr. **Shapiro**. Senator, the safeguard against biased or inaccurate research is the publication of the data from that research in journals such as the New England Journal of Medicine, which are peer-reviewed, in which independent referees examine the work and determine its suitability for publication. Once it has been published, those data are available to every laboratory in the world to examine, to check, to double-check and to see if those results are replicable.

So that you are not relying, Senator, on the personal good faith of any particular individual. You are relying on the scientific method itself, which is the only basis on which we can sanely and reliably base scientific judgments over the long term.

Senator **Metzenbaum**. Mr. Shapiro, your company provided me with a list of your research, noting at whose request the research was commenced. A large number of these studies were requested by a Professor Stegink of Iowa. Let me quote from a UPI story on his research.

"Dr. Louis Stegink, a pediatrics professor at the University of Iowa, who repeatedly produced studies that he says support aspartame's safety, has received more than $1.3 million in research grants and gifts, including lab equipment, from the company since the early Seventies, limited university records show."

There are so many of these studies that would appear to relate to subvention.

Let me ask you this question. Of all the studies that you have funded, have any of them come up with any negative conclusions at all?

Mr. **Shapiro**. I am not aware of any, Senator. And I am not aware of any studies that anyone else has funded which have come up with negative conclusions.

Senator, I feel we are in a Catch-22 position. We are manufacturing and marketing a product which is used by literally hundreds of millions of people around the world. It seems to me we have a responsibility, and we should be taken to task for failing to live up to that responsibility, if we did not go out and seek scientific answers to any scientific question that could be raised. We are doing that.

We welcome sources of funding other than our own. In the case of the Schiffman study, as you noted, there is money from the NIH that was made available to that. There are other places in which researchers can arrange for funding for studies that are deemed to be meritorious other than ourselves. But it seems to me we have an obligation to go out and to continue to fund science in order to make data available to scientists around the world. And I do not see how we can be criticized for doing that, sir.

Senator **Metzenbaum**. No, I am not criticizing you. As a matter of fact, Mr. Shapiro, I am really not attacking you or questioning your integrity or your good faith. As a matter of fact in our discussions, I found you very forthcoming. So I am not saying that you are "the bad guy" standing over there; I do not feel that way at all. I think you are performing your responsible position for your company, and I would hope that we might—I think there are lingering concerns. You say that all the studies have been concluded and that there is nothing more to study, so to speak; there are no more answers that are needed.

I did recite at the very beginning nine separate university studies that continue to raise questions.

And you notice, I have never said, nor do I intend to say on the basis of the scientific data available, that aspartame should be banned. When people have spoken with me about it, I have not said, "Absolutely do not use it." I have said, "If you use it, just limit it," that I think that the question is the amount.

Let me ask you this question. Would Searle, Nutrasweet Company, oppose the concept of labelling the amount of aspartame in a product on the label?

Mr. **Shapiro**. Senator, when we have discussed this in the past, I think what I have tried to say is that in general, we would favor providing as much information to consumers as they can use in making intelligent decisions about what to eat and what to feed their families.

I think there is no basis on anything you have heard today or anything that exists in the scientific record for singling out aspartame as an ingredient as to which quantitative labelling is appropriate, when many other ingredients in the food system are not quantitatively labelled.

I would certainly have no objection as a citizen or as a matter of principle to legislation that said people are entitled to know how much of everything is in everything they eat. It is impossible, it seems to me, to argue with that as a matter of principle.

But I do object and object strongly to singling out aspartame as though there were some special set of issues concerning aspartame when the scientific record is quite clear that there are not.

Senator **Metzenbaum**. What are the company's plans with respect to independent tests, clinical tests, as pertains to use of aspartame?

Mr. **Shapiro**. We have, I think, submitted to your staff a list of studies which are ongoing. We continue to have a program in which we fund through grants additional research, some of which is clinical, and we expect to continue to do that. We are in the process now of looking at 1988 and determining studies to be funded for that year.

[Additional material supplied for the record follows:]

ASPARTAME VICTIMS & THEIR FRIENDS
TEXAS CHAPTER
P. O. BOX 780634
DALLAS, TEXAS 75378
(214)352-4268 (904)351-2086

My name is Mary Nash Stoddard. I live in Dallas, Tx., and I am the founder of the Texas Chapter of the Aspartame Consumer Safety Network. Since going public with my story about the drastic reaction I had to aspartame in 1985-86 (an article was published in the July 27, 1987 edition of the Dallas Times Herald), I have had an opportunity to reach thousands of people via TV interviews, guest appearances on radio talk shows, and personal appearances on behalf of the National Consumer Safety Network. I have supported my endeavors strictly with my own limited private funds, because of a strong personal committment.

One of my main concerns is that the number of people who are being affected by this chemical are not getting their reactions reported and officially tallyed by the proper agency, the FDA. Callers are being mislead or misinformed by individuals in the Regional FDA office in Dallas/Fort Worth. For example:

Debbie Booty - Diagnosed this year with a brain tumor. Drank 8-10 cans daily of Diet Coke. She called the Dallas FDA. They told her NutraSweet could not possibly be her problem. She believes that it is.

Joye Jones - Was told by FDA that NutraSweet was very safe. She had a bad reaction to it and knew better.

Larry Taylor - Anesthetist who has had seizures related to aspartame. FDA in Dallas gave him the national AIDS hotline number for more information.

Gail Foshee - Experienced drastic aspartame reaction. When she called the Dallas FDA in Oct., 1987, they told her it was safe, and that Mary Stoddard was working for the sugar lobby.

Mary Stoddard - My own personal experiences with the FDA are a virtual horror story. My first call to their Dallas office put me in touch with a Mrs. Hazel Wallace their Consumer Affairs person. Her "official" line was that a very few people were "sensitive" to aspartame as people were to shellfish, etc. However, she went on the relate to me the story of her own college-age daughter who drank lots of Diet Coke, and was diagnosed two years ago with a brain tumor and had two surgeries for it after blacking out, seizures, etc. This once-aspiring concert pianist is left with one hand that is useless and draws up to her shoulder at off times. Off the record, she thought aspartame might be responsible for her problems. She promised to set up a public meeting between our group and the Reg. Director this fall. So far, nothing has come of that.

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DALLAS, TEXAS 75378
(214)352-4268 (904)351-2086

After my article appeared, I was asked to do a Dallas radio talk show with host David Gold and co-guest, D. Heelton, Reg. Director of the FDA in Dallas. During the course of this popular show which had thousands of listeners that day, Mr. Heelton lost his composure, called me a liar on the air, and accused me of making serious libelous statements when I said Arthur Hull Hays, Jr. went to work for Burston-Marsteller the Nutra-Sweet pr firm mere months after approving aspartame for aquaeous solution in 1983. This is a matter of public record he flatly denied.

In August of 1987, I decided out of curiosity to call the Reg. FDA office in Dallas, just to see what they were telling people. Romana Farchee told me not to worry - NutraSweet was perfectly safe, like bananas and milk - two amino acids, the building blocks of life. She couldn't remember getting more than a "few" complaints in all her years with the FDA. She drinks it herself, and almost sounded like a TV commercial for the Nutra-Sweet products.

My concern is that most individuals would never pursue registering a complaint after this sort of treatment during a call to the FDA.

Also, how many patients with reactions are going to associate them with consumption of something our Government has approved. Doctors, for the most part, certainly do not make the connection, so how can the patient? Most of the time it happens by accidental re-exposure to aspartame and a distinct return of the symptoms, as happened in my case.

Respectfully yours,

Mary Stoddard

Mary Nash Stoddard
Pres., Texas Chapter
Aspartame Consumer Safety Network
10564 Cox Lane
Dallas, Tx. 75229
214/352-4268

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

OCT 30 1987

Senator Howard M. Metzenbaum,
United States Senate
140 Russell Senate Office Bulding,
Washington, DC, 20510.

Dear Senator Metzenbaum,

The following is in response to a request for comments addressed to me by Mr. James C. Wagoner of your Office in reference to the safety of the artificial sweetener aspartame, known commercially as Nutrasweet.

As you may know, during my service with the FDA from 1964 to 1979 I participated along with others in an extensive investigation of the quality of experimental studies carried out by or for the G.D. Searle & Co. of Skokie, Ill. Inasmuch as I had participated both in the "on-site" investigations at G.D. Searle & Co., as well as in the evaluation of the findings that emerged, my signature along with those of others appears on the final report of that FDA investigation (known also as the Searle Task Force Report) which was dated March the 24th, 1976.

In early 1979 I was transferred for duty from the FDA to the EPA to assume a position involving a promotion for me. My comments here ought not be taken to imply in any way that they represent the views of the EPA since this agency has no regulatory concerns whatsoever in the area of food additives; rather, such comments of mine represent strictly my own views.

During that 1975 FDA investigation at G.D. Searle & Co. and at a number of their contractors, a total of 25 distinct experimental studies were intensively audited. Almost half of those 25 studies (11, to be exact) were carried out for aspartame with the remaining 14 studies having been distributed amongst 6 drug products manufactured by G.D. Searle & Co. It is worthy of note that the conduct of all experimental studies by that firm, regardless whether they entailed food additives or drug products, was the responsibility of a single group in the G.D. Searle & Co.'s organization:- the Pathology-Toxicology or Path-Tox Department. Practices that were noted in connection with any given such study were quite likely to have been noted also for other studies that were audited, and this was a situation which was in no way unexpected:- after all, the set of all such studies executed by that firm from about 1968 to the mid 1970's were conducted in essentially the same facilities, by virtually the same technicians, professional workers and supervisors, and the nature of such studies does not differ much whether a food additive or a drug product is being tested for safety in laboratory animals. It is in this sense, therefore, that the overall conclusions summarized at the beginning of the Searle Task Force Report have relevance to all the studies audited in 1975 (whether they had reference to aspartame or to any of the six drug products of Searle's) and, by extension, to the totality of experimental studies carried out by that firm around that time - 1968 to 1975.

The FDA's Task Force Report starts at the top of its page 1 with:-

> "At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the (case of the) GD Searle Company, we have no basis for such reliance now."
>
> "Reliance on a sponsor is justified when FDA has reasonable assurance that the sponsor will: (1) inform the agency of all material results, observations, and conclusions of an experiment, (2) report fully and completely all of the conditions and circumstances under which an experiment was conducted, and (3) submit its reports to the FDA in a timely fashion so that measures to protect the public health and safety can be taken promptly when warranted. Through our efforts, we have uncovered serious deficiencies in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products."
>
> "Searle has not met the above criteria on a number of occasions and in a number of ways. We have noted that Searle has not submitted all the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product. Some of our findings suggest an attitude of disregard for FDA's mission of protection of the public health by selectively reporting the results of studies in a manner which allays the concerns of questions of an FDA reviewer. Finally, we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed, or inaccurately analyzed or reported."
>
> "While a single discrepancy, error, or inconsistency in any given study may not be significant in and of itself, the cumulative findings of problems within and across the studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies. We have attempted to analyze and characterize the problems and to determine why they are so pervasive

in the studies we investigated."

> "Unreliability in Searle's animal research does not imply, however, that its animal studies have provided no useful information on the safety of its products. Poorly controlled experiments containing random errors blur the differences between treated and control animals and increase the difficulty of discriminating between the two populations to detect a product-induced effect. A positive finding of toxicity in the test animals in a poorly controlled study provides a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that the results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product."

In addition to those general comments and references to no basis for reliance on reports generated by the GD Searle Company, serious deficiencies in Searle's operations and practices, Searle's integrity, Searle's selectively reporting the results, poorly conceived, carelessly executed and inacurately analyzed or reported experiments at Searle's, a pattern of conduct which compromises the scientific integrity of the studies, pervasive problems in the Searle studies, their unreliability, etc., which apply across the board to all studies investigated, there are a number of additional problems that attach specifically to the aspartame studies. These are discussed in the FDA's Searle Task Force Report in its

page 25 - paragraph 1 - on the identity of the material tested;

page 26 - last para. - on the excision of tumor masses ante-mortem and writing the protocol after the start of a study;

page 31 - paragraph 2 - on Searle tactics designed to obtain FDA approval for aspartame;

page 32 - last para. - on continuity of personnel at Searle and on the adequacy of their training and supervision of such personnel;

page 33 - paragraph 2 - on practices which could compromise the study;

- paragraph 3 - on improper departure from protocol specifications on age of the animals used;

page 34 - paragraph 2 - on deviations from protocol at Hazleton Laboratories;

page 36 - paragraph 3 - on the lack of concern both at Searle and at Hazleton Laboratories over the homogeneity, or stability of the ingredient-diet mixture; subsequent paragraphs deal with the same sort of problem at Hazleton Laboratories and it is concluded that "there is no way in which it can be assured that animals received the intended dosage.";

page 39 - paragraph 1 - on the improper use of pesticides in the areas where the studies were carried out; on the condition of the blenders used to mix the test agent in the diet; on the lack of records on mixing operations; on the conditions of the labels of the mixtures; on the lack of inventories of the test substance;

page 42 - paragraph 1 - on the records kept of the observations made and on the numerous errors and inconsistencies amongst observations and findings;

page 47 - near bottom - on the impact of the errors in the records of observations;

page 51 - paragraph 1 - on the excision of tumor masses; see also page 52, paragraph 1 there for the impropriety of this practice;

page 52 - last para: - on the "substantial" loss in pathology information due to autolysis, fixation "in toto", etc.

page 55 - top - on the impropriety of changing a prosector's observations by others who did not participate in examining the carcasses of the animals;

page 57 - paragraph 2 - on the poor quality of material prepared for microscopic examination of the tissues;

page 60 - paragraph 3 - on observations being reported for material that never existed; this problem was noted at both Searle and Hazleton Laboratories;

page 62 - paragraph 2 - on the lack of training by the "professional" scientists making observations in teratogenicity studies;

page 64 - paragraph 3 - on the abysmal quality of the aspartame teratology and reproduction studies and on an evaluation of these by a leading international British expert in this area;

page 66 - paragraph 3 - on the serious problems with the Waisman study of Aspartame in monkeys;

page 80 - top - on the false values presented by Searle on observations collected during the aspartame studies in hamsters, with reference to blood, clinical chemistry, etc., and the improper filtering of results from the 115 week rat study with aspartame.

It should be pointed out that the Task Force Report detailing those general conclusions as well as those that relate specifically to the aspartame studies are not merely the views of the members of the Task Force itself. That Task Force operated under the direction of a Steering Committee composed of a number of FDA Bureau Directors as well as others and the Chairman of that Committee was none other than the FDA Commissioner himself. In fact the Task Force Report was addressed to the Commisssioner in his capacity as Chairman of the Steering Committee, and, it seems clear that both the Committee and the Commissioner accepted that report and transmitted it to the United States Senate as an institutional FDA report without changing in it as much as a semicolon. The following are quotes from pages 3 and 4 of the record of hearings of April 8-9 and July 10, 1976, held by Sen. Edward Kennedy, Chairman, Subcommittee on Administrative Practice and Procedure, Committee on the Judiciary, and Chairman, Subcommittee on Health, Committee on Labor and Public Health:-

page 3 of the record - Commissioner Schmidt of the FDA :- "today I would like to report to you the final results of the Food and Drug Administration's (FDA) detailed investigation of animal studies performed by Searle..." (emphasis added);

page 4 of the record - Senator Kennedy (addressing Commissioner Schmidt):- "Let me ask you this. These are the conclusions of the (Task Force appointed to that) study. Do you agree with those conclusions ?"

Dr. Schmidt:- "Yes I do."

Senator Kennedy:- "Yes, you do. Is this the first time, to your knowledge, that such a problem has been uncovered of this magnitude by the Food and Drug Administration ?"

Dr. Schmidt:- "It is certainly the first time that such an extensive and detailed examination of this kind has taken place. We have never before conducted such an examination as we did at Searle."

"From time to time, we have been aware of isolated problems, but we were not aware of the extent of the problem in one pharmaceutical house..."

Given those conclusions reached on the quality of Searle experimental studies in general and of the aspartame studies in particular, as we have seen above, by both the FDA as an institution and its Commissioner in 1976, how is it possible for another Commissioner in July, 1981, to reapprove the use of aspartame being marketed in dry foods ? How is it possible for yet another Commissioner two years later, in July, 1983, to have extended such approval for marketing aspartame also in carbonated beverages ? Such approvals were based on largely the very same studies that were examined by the Task Force in 1975-76.

It seems to me that no amount of additional examinations of pathology material such as undertaken by the UAREP and others, no additional statistical analyses carried out on the data, and no judgmental evaluations or interpretations of any data arising from those studies can in any way rectify the basic problem expressed by the Task Force, i.e., the FDA itself: in the absence of reasonable expectation that the experimental animals were administered the correct dosages of the test agent, any observational data carried out on those animals must be regarded as questionable or flawed. This is to say nothing of all the myriad of other problems involving the competence of those conducting such studies, and the care they exercised in their execution. Once a study is carried out and the test animals are disposed of, all that remains are a number of tiny bits of tissue preserved from their organs for microscopic examination and the written records of observations made by those who actually carried out that study. While the tissues themselves can be examined by others long after the remains of those animals no longer exist, the reliability of the written records has already been found to be unacceptable in a great variety of ways. Clearly, there is no way that even the most competent scientists can make any new observations on those animals at a time subsequent to the conduct of the study. Once a study is compromised in its execution, it is beyond salvation by anyone.

Even with respect to those small portions of tissue preserved for microscopic examination for an indefinite period of time after any study is completed there are serious problems as presented in the 1976 FDA report with respect to Searle studies in general and for the aspartame studies in particular:- there is little if any assurance that such samples of tissues as were preserved actually originate from the specific animals said by Searle or Hazleton to have been their source (see the discussion on page 57 paragraph 2 et seq.) Furthermore, due to the unacceptably high rate of post-mortem autolysis, a great many such tissues were not collected at all from the experimental animals. In any such study of even a few hundred test animals, it takes no more than a dozen or so of them to exhibit a particular lesion (such as brain tumors, for instance) where missing no more than one or two animals manifesting such tumors in any given exposure group may well make the difference whether that particular lesion is or is not significantly associated with the test agent, i.e., aspartame or any of its related chemicals.

Following the Senate hearings in the Spring and Summer of 1976, during the Winter beginning in that year the FDA began negotiating with GD Searle & Co. on retaining the UAREP (Universities Associated with Research and Education in Pathology), a private organization, on the feasibility of investigating a number of other Searle studies with aspartame. When I heard of those negotiations being in effect, I wrote a memorandum to Mr. Carl Sharp, the Chairman of the FDA's Searle Task Force, on November the 4th, 1976. A copy of it is given here as Attachment 1, and my apprehensions over such plans is clearly evident there. Basically, they amounted to the fact that the UAREP was totally unsuited for such task since it had never before engaged in anything like it and I also objected to the idea that Searle was to fund that particular activity by the UAREP. As mentioned there, the FDA had just received a supplemental appropriation from the US Congress for the express purpose of expanding its own activities in that very area of investigating the conduct of such experimental studies by the regulated industry. Under that appropriation (which came to some $16,000,000) a great number of additional investigators were hired and trained for this particular task by the FDA.

A few months prior to the UAREP beginning its investigations in August of 1977, in April of that same year, yet another FDA investigation of three aspartame studies conducted by GD Searle & Co. was undertaken. The 76-page report of that investigation (also known as the Bressler report, after the name of the leader of the investigative team, Mr. Jerome Bressler, a compliance officer in the FDA's Chicago District) reveals with reference to a single one of those studies (the 115-week experiment in rats exposed to DKP or diketopiperazine, a breakdown product of aspartame) the following:-

- substitutions of some of the animals in that study;
- the presence of intercurrent disease amongst the test animals and the administration of drugs to combat this, neither of which were completely reported to the FDA;
- incomplete examination of tissues from the experimental animals;
- excision of tissue masses likely to be tumors from live animals during the study;
- absence of batch records for the mixing of the test substance into the diet of the test animals;
- incomplete stability studies for the agent on test;
- absence of homogeneity studies for the agent on test;
- deficiencies in the methods of chemical assay for the actual DKP that was mixed into the diet of the experimental rats;
- problems with the dosage of the DKP that was given to those rats;
- problems with the fixation-in-toto and autolysis;
- failure to report to the FDA all tissue masses (likely to be tumors) which were found in the experimental rats;

- failure to report to the FDA all internal tumors present in the experimental rats, e.g., polyps in the uterus (Animal K9MF), ovary neoplasms (Animals H10CF, H19CF, and H7HF) as well as other lesions (Animal D29CF);

- inconsistencies between different parts of the report on this study submitted by GD Searle & Co. to the FDA on the precise nature of the lesions manifested by the test rats;

- numerous transcription errors in that report.

Interestingly and most important, the Bressler investigating group found not only that no homogeneity tests were conducted by GD Searle & Co. on the mixture of the test agent within the animals' diet, but they actually obtained direct evidence that in fact the distribution of the test agent in that diet was clearly not homogeneous due to failure to have the test agent ground in a sufficiently fine manner. Descriptive remarks on this issue were found by the FDA investigators in a notebook kept by Searle personnel on observations made during the study, as was a Polaroid photograph taken by the same Searle technicians and which clearly shows the test agent in the form of coarse particles within the animals' diet. It follows that the experimental rats could have consumed their feed without actually touching the DKP and, consequently, no-one can state with any assurance whatsoever just how much DKP (if any) those rats were actually exposed to in the course of that study. Evidence such as this obtained by the FDA investigators seems to me to have been crucial to the interpretation of any findings or observations reported by Searle.

On page 32 of the GAO report one can read the views of the FDA's Centre for Food Safey and Applied Nutrition (CFSAN) on the findings of the investigators. To me these read like a script written for Abbott and Costello in the sense of their having their perceptions inside-out or upside-down - "the diets may have been homogeneous because of a dose-related increase in the incidence of uterine polyps and decrease in blood cholesterol levels" (a clear non-sequitur, such as one almost never encounters in real life); on the problem with autolysis of the tissues the CFSAN felt "they could not determine whether the results would have been altered if these tissues had been obtained before autolysis (an obvious instance of placing the burden of proof that a study is unsound on the Government rather than requiring the petitioner for approval of a food additive to demonstrate, as the Law requires, that any study is of sound quality); the observation by the investigators that 329 fetuses were examined in two days by a single person (a clear impossibility) was laid aside by the CFSAN with another non-sequitur:- that "the Searle scientist who performed these examinations estimated that he examined about 30 fetuses a day..."; on the fact that an insufficient number of sections were made out of the heart, the CFSAN observed:- "...while there was no evidence that the study was compromised by this issue, the practice of not making enough sections through the organs, as specified in the protocol, did not preclude a possible failure to observe abnormalities which may have occured."

Despite all these problems, at least some of which undermined or compromised the study in an unredeeming manner, apparently the CFSAN and the FDA Commissioner found the quality of those three studies reported on by the Bressler investigating group as being in fact of an acceptable nature and GD Searle & Co. were notified to this effect in September, 1977.

The investigation undertaken by the UAREP began in August, 1977. After reading the report of that group, it became painfully clear to me that the misgivings which I foresaw in November 1976 (see Attachment 1 here) were indeed justified and my worst fears were eventually realized. If one compares the kind of detailed and painstaking findings made by the professional investigators from the FDA both in 1975 and in 1977 with the rather amateurish activities by the UAREP outlined in their report, the contrast between these could hardly have been greater. Of course, inasmuch as GD Searle had paid for the UAREP investigation, the cost of it for the FDA was nil; what the FDA got in return for its money, was not worth much more than this.

Perhaps the most disappointing aspect of this entire fiasco with the quality or reliability of the experimental studies with aspartame was the failure of the Public Board of Inquiry (PBOI) to consider these aspects in their deliberations. The PBOI expressly declined to do so even after the principal objectors to the approval of aspartame for marketing, Mr. James Turner and Dr. John Olney, asked for such consideration. To me it seems almost beyond belief that a collection of scientists can sit in judgment over the interpretations to be made on a set of results arising from certain studies, not only failing to consider the adequacy of the conduct of those studies but actually refusing to do so.

Given this sort of circumstance, it should not come as a surpise to anyone that eventually the Commissioner of the FDA finally reapproved aspartame for marketing even though his own panel of experts were divided over the issue whether this particular food additive had been shown in a reasonable manner to be safe.

As mentioned in the GAO report (page 12 there) "The Federal Food, Drug, and Cosmetic Act does not specifically define 'safety'. However, the legislative history of the Food Additives Amendment indicates that safety means 'proof of a reasonable certainty that no harm will result from the proposed use of an additive'." It is intuitively clear to anyone that no "reasonable certainty" can attach to any results emanating from studies as profoundly flawed as the Commissioner of the FDA had determined in 1976 and as amply reconfirmed since then.

This concludes my remarks on the quality or reliability of the experimental studies with aspartame carried out by the GD Searle & Co. or by the contractors working under the direction of that firm

Since Mr. Wagoner of your Office has requested my comments in a very short period of time, I am expediting this letter to you now; however, I plan to send you in the very near future an additional communication where two other issues are discussed in some detail:- the problem with the brain tumors induced by aspartame and that with the FDA's having set a very high (and, to my view, clearly dangerous) level of the Acceptable Daily Intake, or ADI, for this particular food additive in the diet of humans.

Finally, I wish to state here that, quite aside from my professional background as a scientist and speaking merely as an individual citizen, I am grateful for the concern you have had over the safety of aspartame for many years now; as such, I wish to thank you for having given me this opportunity of being of some service to you. With best wishes for the future, I remain, Senator Metzenbaum,

sincerely yours,

M. Adrian Gross,
Senior Science Advisor,
Benefits and Use Division,
Office of Pesticide Programs.

Encl.:- Attachment 1 (3 pages)

I certify that the signature above is my own and that, to the best of my knowledge, the contents of this letter are true and accurate.

Sworn to and subscribed before me this 30 day of October, 1987.

Commonwealth of Virginia
County of Arlington
8-20-91

Sharyn J. Hedgeler

Attachment 1 (3 pages) + tables 38

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Mr. Carl Sharp

DATE: [illegible] 1976

FROM : M. Adrian Gross

SUBJECT: Draft Agreement for Validation of Searle Aspartame Studies

The following are some comments which you requested on the document under reference as well as on the cover memorandum Wylie/Gardner dated November 1, 1976.

I must confess that I became deeply disturbed on reading this effort - last July 14th in a telephone conversation I had with Commissioner Schmidt during which I stated my reservations about this entire plan, he assured me that whatever is being contemplated in this area will be undertaken in full knowledge of and consultation with some of us who were intimately involved with the Searle investigation and that whatever is finally accepted will be of such nature as not to jeopardize or undermine all of our previous work. Given this kind of background I suffered a rude shock by the proposed plan in front of us at this time.

Let us put this matter in some perspective by establishing the basic facts here. The Searle investigation which started in the Fall of 1975 can be viewed as an investigation "for cause" following the discovery of certain improprieties in the conduct of animal studies during preliminary inspections in 1974 and in the first half of 1975. The report of the Task Force submitted in March 1976 in essence constituted a stinging indictment of Searle and it contained various recommendations for regulatory action including referral to the Justice Department for review of possible criminal violations of the law.

The Aspartame studies to which we have reference here are nothing but an extension of the studies which were reviewed by the Task Force. I see no essential difference between them and any of the studies already investigated. In the meantime this Agency has received a substantial amount of additional funding for the express purpose of monitoring the quality of research carried out by regulated industry in a much expanded fashion. As part of this program, there has been a marked degree of effort, time and money expended on setting up sundry task forces, steering committees, training courses for investigators, "surveillance" inspections, regulations for good laboratory practices, compliance programs, etc.

Yet, notwithstanding any of this, now that the Agency is confronted with the need of completing what it started out to do in this Searle matter, we seem to be turning to an outside group of questionable capability in this area:- the UAREP. I know absolutely nothing of the past experience of this outfit to carry out investigations of this sort - perhaps, whoever it was that selected this group to carry out our responsibilities for us might be as kind as to enlighten us on this point. I noted the name of Dr. Stowell associated with this organization - I have known Dr. Stowell for many years now from the time he was Scientific Director of the Armed Forces Institute of Pathology and I can readily agree that he has impeccable credentials and a remarkable achievement in his own field of pathology; as far as investigations of the sort that we are concerned with here, however, I would judge him to be a complete neophyte in this particular area. I also know nothing of the qualifications of the investigators which will be selected by Dr. Stowell or others at UAREP to do the actual "hands-on" part of the investigation - we need additional details here but I would doubt very much that UAREP could come up with a number of workers who are both experienced and competent in matters of this sort.

Speaking as a pathologist, I seriously question the wisdom of selecting a group of pathologists to oversee the kind of investigations that are called for here; pathology problems do not constitute but a small part of the difficulties involved in situations such as these. My own experience is that, as a rule, controversial technical aspects in pathology proper (such as whether any particular characterization of any given lesion is a proper one or not) are seldom an important factor in a determination whether any study contains serious flaws. This has been amply demonstrated in the extensive Searle investigation as well as in other investigations currently under way in the Bureau of Drugs. I have great difficulties in visualizing pathologists conducting a searching examination of a variety of records which have nothing to do with pathology or closely question a number of administrators, laboratory technicians or aids, animal caretakers, etc., on their practices, on details of their tasks, adequacy of their observations and so on.

I would not like to generate the impression here that scientific expertise in pathology or in any other scientific field associated with studies like these could or should be totally ignored. Far from it. However, the concept under which we have operated ever since I can remember is that investigations are best handled by trained and experienced investigators. Where there is a need to address certain scientific problems which transcend the capabilities of the investigators, the practice has always been for appropriately qualified specialists from the various Bureaus of the FDA to assist the investigators; in those few cases where outstanding technical difficulties beyond the capabilities of Agency scientists are required, we have not refrained in the past from using help from outside and I should hope we shall continue to do so in the future. But this help provided by scientists on an ad-hoc basis and only where it is required is an entirely different matter than having scientists direct the actual course of the investigation. While I believe it is entirely proper (in fact preferable) to have scientists evaluate the scientific impact of a set of findings, I cannot see professional scientists do the job of professional investigators any more than I could see members of a legal society doing the work of detectives or policemen in investigating various aspects of a specific crime.

It disturbs me to see from the draft we have here that the rôle of what is termed the "FDA Monitor" will be reduced to little more than having this person be present during communications between UAREP and Searle; I find this kind of prospect ludicrous and I do not understand the need for it.

What I understand even less is why Searle should offer or be asked to pay the cost of this entire operation to the investigative agent in a direct manner; why is there a necessity for this body, UAREP, to enter into any kind of formal contract with Searle and why are we expected to co-sign such a contract ? The fact that Searle will pay for this cannot but give them some kind of decision-making role as is evident from merely reading the terms of this proposed contract. It seems to me that no-one except the FDA can have the responsibility for undertaking this kind of work - this is our mission and we are being paid from public funds to carry it out.

Although, as expressed above, there is much I do not understand about this entire plan, particularly its basic raison d'être, there is something here that I appreciate fully:- this is the statement at the top of page two of Wylie's memorandum:- "Searle understandably continues to press for the expediting of this agreement."

I would suggest that implementation of this contract can have only one of two predictable outcomes which are mutually exclusive:-

a) There are serious improprieties in the conduct of these studies. If this is the case, I would submit that inexperienced outside scientists selected by an outside agency under contract to the firm which is the object of the investigation, will have a markedly reduced probability of detecting such improprieties;

b) There are no serious improprieties in the conduct of these studies If this is the case, it would necessarily follow that any report written by the "investigators" would not signal the presence of any such improprieties. But, if so, for exactly the same reasons as listed above, such a report may well be interpreted as being nothing short of an improper whitewash.

My recommendation is simply that this entire plan be aborted forthwith, and that we proceed with this matter in the way we are supposed to; this is the way we have handled things like this in the past and the way we anticipate to operate in the future.

M. Adrian Gross
HFD-108

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 3 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Senator Howard M. Metzenbaum,
United States Senate,
140 Russell Senate Office Building,
Washington, DC, 20510.

Dear Senator Metzenbaum,

The following represents a continuation of my letter to you of last week, October the 30th, 1987. In that letter I discussed the many serious problems with the quality or reliability of the experimental studies with aspartame carried out by or for G.D. Searle & Co.; I noted there that in 1976, the FDA Commissioner at that time, Dr. Alexander Schmidt, speaking for the FDA as an agency, publicly stated that he agreed with a set of conclusions, the first of which was that the FDA had no basis for reliance on the quality of studies generated by or for that firm.

Once such a determination is made at the highest level of the FDA, it seems bizarre, to say the least, that essentially the same set of studies could provide a foundation for a subsequent decision that those studies in fact had demonstrated the safety of aspartame with "reasonable certainty" as required by the Food Additive Amendment of the Federal Food, Drugs, and Cosmetics Act. As the television commercials for Weyerheauser, the "tree-growing company", keep telling us:- "once the eagles are gone, they are gone."

Much the same is true also for experimental or laboratory rats:- once they are gone, no one can bring them back for an interview to ask them how much, if any, aspartame or DKP they had ingested while the experimental studies in which they had participated were in progress and, without such essential information, examination of their preserved tissues by even the most skillful and competent of pathologists becomes largely a meaningless exercise which cannot in any way resurrect in Phoenix-like fashion the value of those studies.

However, having said all of this, let us assume that in fact those studies were of an acceptable quality; let us pretend that the test animals were actually exposed qualitatively and quantitatively to what G.D. Searle & Co. would have us believe that they were exposed; that there was no post-mortem autolysis of their carcasses rendering vast numbers of their tissues to a state unsuitable for pathology examination; that the technicians involved in the conduct of those studies were fully trained, competent, and adequately supervised to make observations on those animals prior to their death; that the same was true with respect to the observations made after their death; that in fact those technicians actually made proper such observations; that the proper samples of tissues with grossly observed lesions were in fact collected for additional microscopic examination; that the identity of such tissue specimens corresponded (as they should) to the identity of each animal that was their source, etc. In short, let us make believe in a spirit of Halloween that nothing which was uncovered for the aspartame studies by the FDA investigations of 1975 and 1977 was actually true, i.e., that in fact we are dealing here with studies of an absolutely perfect quality or reliability. Of course, such assumptions belong to the domain of Fantasyland, but, nevertheless, let us play this little game for a while.

Under such highly speculative hypothetical conditions, let us now ask again whether aspartame can be viewed as being safe with "reasonable certainty".

To answer this question, let us focus for a moment on the pathology examinations carried out not by the pathologists originally retained by GD Searle & Co. (those of the Experimental Pathology Laboratories, or EPL) who examined the tissues from the rats in the Two-Year Rat Study) but, rather, on the examinations carried out by the expert pathologists in the UAREP. Although in my last letter addressed to you last week I referred to the investigative efforts of the UAREP as being "amateurish" by comparison with those of the professional investigators in the FDA, I have no reason to question or criticize in any way the competence of UAREP pathologists in their own specialty where they had examined first-hand tissue specimens said to have been collected from the animals in that study.

The UAREP report (Volume 2, Chapter IV, dealing with that particular study, reveals in Appendix IV-21 on its page 393 et seq. the animals which were found by the UAREP pathologists to have harbored brain tumors:-

Group	Sex	Path.No.	Animal No.	Type of brain tumor	Weeks to death
1	M	64-603	83-651	Astrocytoma	104
2	M	64-775	83-745	Astrocytoma	104
3	M	64-764	83-837	Astrocytoma	76
4	M	64-707	83-919	Astrocytoma	104
		64-712	83-888	Oligodendroglioma	59
		64-713	83-892	Astrocytoma	49
		64-715	83-895	Astrocytoma	100
5	M	none			

(continued on next page)

page three

(Table continued from previous page)

Group	Sex	Path. No.	Animal No.	Type of brain tumor	Weeks to death
1	F	none			
2	F	64-989	83-769	Astrocytoma	104
		65-011	83-766	Astrocytoma	69
3	F	none			
4	F	64-925	83-934	Astrocytoma	85
5	F	64-881	84-010	Medulloblastoma/ meningeal sarcoma	13
		64-888	84-019	Astrocytoma	67

Altogether the table just above lists a total of 12 animals with brain tumors, 7 males and 5 females; for both sexes there are 1 in Group 1, 3 in Group 2, 1 in Group 3, 5 in Group 4, and 2 in Group 5 for a total of 12. Note that the GAO report which refers to those animals at the bottom of its page 45 is in error in that it lists 4 (rather than 3) animals with brain tumors in Group 2 (the low dosage group). Because of this error, the GAO's Figure 4.1 on page 46 of its report is somewhat misleading.

The GAO report also indicates under item (2) on its page 34:-
"According to UAREP's president at the time of its review"

> "...the thing that impressed (UAREP) throughout the study,... which is reflected in our final statements and conclusions, was that the interpretation of the experimental results by previous observers did not really differ very significantly from ours following our review of the material."

Yet Appendix IV-25 beginning on page 446 of the UAREP report represents a 6-page table entitled "Significant Discrepancies Between Histopathologic Diagnoses By UAREP and EPL", the last mentioned having been, as stated above, the "previous observers", i.e., the pathologists originally retained by GD Searle & Co. to examine those tissues and whose report was submitted by that firm to the FDA in support of their petition to have aspartame approved for marketing. In that table I have counted some 207 such "significant discrepancies" between the diagnoses of the UAREP and EPL and these involve some 162 animals or 37% of all the 440 animals in that study. This was not reported by the GAO representatives who apparently were content with merely chatting with the UAREP president about his reminiscences of some 10 years ago.

Moreover, that same UAREP report reveals in that very same Appendix IV-25 as cited above for the 12 animals with brain tumors the characterizations or diagnoses reached by the pathologists from the EPL:-

for Animal No. 83-651 with an astrocytoma of the brain
EPL lists the brain as unremarkable;

for animal No. 83-745 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-837 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-919 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-888 with an oligodendroglioma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-892 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-895 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-769 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-766 with an astrocytoma of the brain
EPL lists no comparable diagnosis;

for animal No. 83-934 with an astrocytoma of the brain
EPL lists an ependymoma i.e., a different
kind of brain tumor;

for animal No. 84-010 with a medulloblastoma/meningeal sarcoma of
the brain, EPL lists a meningioma i.e., a
tumor of the membranes covering the brain;

for animal No. 84-019 with an astrocytoma of the brain
there was no discrepancy in the EPL diagnosis.

In other words, for the 12 animals identified as having brain tumors in this study by the UAREP pathologists, EPL pathologists (i.e., the "previous observers" as the president of the UAREP has it) had completely missed no less than 9 or 75% of these. Such difference between the diagnoses of those two groups cannot by any stretch of the imagination be interpreted by any reasonable person as being "not very significant" as that same president of the UAREP is quoted by the GAO to have stated. Incidentally, the GAO representatives themselves also failed in their report to highlight this tremendous difference between the diagnoses of the UAREP and the EPL.

Furthermore, Appendix IV-20 on page 391 of that same UAREP report reveals in the first row of the table on that specific page that GD Searle & Co. or their agents had provided to the subcontracting EPL pathologists, i.e., to those whose report that firm had originally submitted to the FDA:-

a) only 8 (or only 10%) of the brain sections for the 80 animals in Group 2;

b) only 7 (or only less than 9%) of the brain sections for the 80 animals in Group 3;

c) only 5 (or only less than 7%) of the brain sections for the 80 animals in Group 4;

and the UAREP were provided with the brain sections of 2 fewer animals than were provided to the EPL. Again, this is another little wrinkle not highlighted in the GAO report.

This, quite by itself, is sufficiently eloquent on just how G.D. Searle & Co. saw fit to discharge their responsibilities in reporting fully and completely their results of the Two Year Rat Study with aspartame to the FDA; it is just as eloquent on precisely how thoroughly the Bureau of Foods of the FDA (the predecessor of the CFSAN) had reviewed the data emanating from that study prior to its initial approval in 1974 for the marketing of that food additive.

I note at the bottom of page 54 in the GAO report that the CFSAN had objected to the medulloblastoma that was noted in a female rat at the top exposure level on the grounds that "it was unlikely aspartame caused this tumor". Such statement would imply that aspartame had caused all the other tumors (the nine astrocytomas and the solitary oligodendroglioma noted in animals exposed to it) which is vastly more than enough to lead to a conclusion that, because of this, it cannot be regarded as being a safe food additive. The reasons for such conclusion by the CFSAN appear in the first paragraph of page 46 of the GAO report. As is also true for many of the other arguments advanced by the CFSAN and by G.D. Searle & Co., those reasons are largely speculative and without much merit. Still, to accommodate the CFSAN's views regardless of their validity, I am willing to ignore the occurence of that particular tumor in a female animal at the top exposure level.

If we are to analyze the distribution of the rest of those brain tumors, we ought ignore also the response of any animals at the top level of exposure (Group 5) on the grounds that competing toxicity may well have inhibited the expression of brain tumors in the animals in that group.

Accordingly we have for the male animals with brain tumors:-

in Group 1 i.e., at 0 mgm/kgm body-weight 1/59 = 1.69% positive rats;

in Group 2 i.e., at 1,000 mgm/kgm body-weight 1/36 = 2.78% positive rats;

in Group 3 i.e., at 2,000 mgm/kgm body-weight 1/40 = 2.50% positive rats;

in Group 4 i.e., at 4,000 mgm/kgm body-weight 4/40 = 10.00% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,019,865 with standard error of only 0.000,009,729,2 leading to a chi square with one degree of freedom for slope as high as 4.118, whose one-sided probability is as low as p = 0.021,217; in other words, the dose-dependent increase in the frequency of brain tumors for the male rats in that study was highly significant and, therefore, attributable to aspartame, the agent on test.

That particular slope of the dose-response function yields the following expected incidences of brain tumors amongst male animals:-

at 0 mgm/kgm body-weight - 0.867%

" 1,000 " - 2.854%

" 2,000 " - 4.840%

" 4,000 " - 8.813%

Note that the four expected values given just above are fairly close to their respective observed values listed near the bottom of the preceding page, which indicates a close fit of the observations to the dose-response or regression function.

If we have reference to the animals of both sexes with brain tumors, we have:-

in Group 1 i.e., at 0 mgm/kgm body-weight 1/118 = 0.847% positive rats;

in Group 2 i.e., at 1,000 mgm/kgm body-weight 3/ 76 = 3.948% positive rats;

in Group 3 i.e., at 2,000 mgm/kgm body-weight 1/ 80 = 1.250% positive rats;

in Group 4 i.e., at 4,000 mgm/kgm body-weight 5/ 80 = 6.250% positive rats;

This particular distribution yields a dose-response slope as high as 0.000,011,578 with standard error of only 0.000,005,831,8 leading to a chi square with one degree of freedom for slope almost as high as the one for merely the male animals, 3.920, with one-sided probability almost as low as that for merely the male animals, p = 0.023,860. The conclusion that follows is identical with that reached above for merely the male animals.

The expected incidences for both sexes are:-

at 0 mgm/kgm body weight - 1.006%

" 1,000 " - 2.164%

" 2,000 " - 3.322%

" 4,000 " - 5.638%

or, again, fairly close agreement to the observed values given just above.

Note that in the analyses outlined above I have *not* combined the response noted at two or more experimental group, as was done by the PBOI and as objected to by the CFSAN.

If we now analyze the data in the same "uncombined" fashion, while still excluding from consideration the medulloblastoma manifested by a female in the top exposure level group, and even if we do consider the poor response of the animals in the top exposure level group (which, as noted, may have been due to competing toxicity interfering with the expression of brain tumors), but consider the so-called "historical control" incidence of brain tumors (49/59,812 cited by Dr. Olney in his Table 2 on page 2 of Part III of his written statement presented to the PBOI as well as the rate of 4/115 positive control animals noted by both the UAREP and the EPL for the Lifetime Toxicity study of aspartame in the rat - see UAREP report, Chapter V, page 559) along with the contemporaneous (local) control rate of 1/118 positive animals of both sexes noted in the Two-Year aspartame study in the rat, we end up with a total of 54/60,045 = 0.090% for the control incidence for both sexes. The weighted average of the exposure level in Group 5 animals was 7,420 mgm/kgm body-weight. Accordingly we would have:-

at 0 mgm/kgm body-weight 54/60,045 = 0.090% rats with brain tumors;

at 1,000 mgm/kgm body-weight 3/ 76 = 3.947% rats with brain tumors;

at 2,000 mgm/kgm body-weight 1/ 80 = 1.250% rats with brain tumors;

at 4,000 mgm/kgm body-weight 5/ 80 = 6.250% rats with brain tumors;

at 7,420 mgm/kgm body-weight 1/ 77 = 1.299% rats with brain tumors.

This distribution yields a slope of the dose-response function as high as 0.000,005,297 with standard error of only 0.000,000,423,4, leading to a chi square with one degree of freedom for slope as high as 156 whose one-sided probability is as low as 4.031E-36, i.e., 4 with 35 zeros ahead of it and to the right of the decimal point. This is nothing short of astronomically high significance.

Alternatively, if one considers merely the contemporaneous or local control value in the two-year rat study with aspartame, 1/118 = 0.85% animals positive for brain tumors, the response at the *lowest* level of exposure, 1,000 mgm/kgm body-weight, 3/76 = 3.95% animals similarly positive for brain tumors, is elevated by comparison with that control rate *more than 4.5 times* which is of borderline significance at p = 0.058,674. The response at the next to the highest level of exposure of 4,000 mgm/kgm body-weight, 5/80 = 6.25% animnals with brain tumors, is elevated *more than 7.3 times* over that same control rate of 0.85%, and this is highly significant at the p = 0.009,975 probability level.

Finally in this entire consideration of significance for the brain tumors, one could set up yet another sort of contrast by making believe that all animals exposed to aspartame were in fact exposed to the highest level tried, 7,420 mgm/kgm body-weight, rather than to various levels beginning at 1,000 mgm/kgm body-weight. This would extend a great deal of the benefit of doubt to aspartame. That particular contrast of 0.090% the control rate versus 10/313 = 3.195% for all exposed animals (still excluding the medulloblastoma objected to by the CFSAN), leads to a chi square adjusted for continuity and with one degree of freedom as high as 254 which is, again, of almost astronomical significance.

In other words, even if if one is willing to give to aspartame a very generous benefit of doubt on the quality or reliability of the two-year study in rats as well as several other considerable benefits of the doubt involved in the test of significance, it still emerges that the rate of brain tumors amongst the animals exposed to it vastly exceeds that for animals not exposed to it and such excess is very highly significant. What this says is that there cannot be any reasonable, or even shadow of a doubt that aspartame had caused such increase in the incidence of brain tumors.

It follows, therefore, that the conclusion of the PBOI and of several members of the FDA Commissioner's panel of experts is the right conclusion, and that reached by the CFSAN and by the FDA Commissioner who overturned the PBOI view in this respect is the wrong conclusion.

As a result of all the considerations above, I would add my full endorsement to the conclusion of the unidentified statistician mentioned in paragraph 3 on page 56 of the GAO report who apparently reached the same conclusion as I did in an independent manner.

I would also support the views of the similarly unidentified carcinogenicity specialist mentioned in paragraph 2 of that same page in the GAO report who felt that the relatively high exposure rates in the two-year rat study with aspartame were a necessary compensation for the relatively low power of this study to detect as significant increases as high as 5% in the brain tumor rate for humans exposed to aspartame, which would constitute a downright catastrophe.

The Acceptable Daily Intake (ADI) of aspartame.

Still under the hypothetical assumption that these experimental studies were of an impecable quality, let us now turn to a different aspect of the interpretation of results arising from them.

Near the bottom of page 60 of the GAO report it is disclosed that the Acceptable Daily Intake (ADI) of aspartame was raised from 20 mgm/kgm body-weight to 50 mgm/kgm body-weight after aspartame was approved for use in carbonated beverages and after it became evident to the FDA that very young children could potentially consume almost 50 mgm/kgm body-weight of it per day.

It appears that the justification for such sudden and considerable increase of 150% in the ADI for aspartame was provided by the results of five clinical studies as well as five other studies published in the literature; however, it is unclear from the GAO report whether any of those studies were of long-term duration (such as a major part of the life- span) - clearly, such studies conducted with humans could not possibly have been of this nature.

To examine whether an ADI of 50 mgm/kgm body-weight can be justifiably regarded as "safe", let us return to the issue of the brain tumors and conduct for these a formal Risk Assessment. Although it has been established here that the incidence of brain tumors in rats was highly significantly related to the dosage of aspartame in the two-year rat study (and, therefore, that aspartame had caused that increase in incidence of brain tumors amongst exposed animals by reference to the rate noted in comparable unexposed ones) such determination of high significance is in fact not a necessary requirement for a formal risk assessment.

I have carried out such risk assessment by utilizing two separate procedures which are widely accepted for this purpose:- the Mantel-Bryan approach (also known as the log-probit method) and the One Hit method of extrapolation.

To extend again the benefit of doubt to aspartame, I have had reference in such assessment to the control rate of brain tumors noted merely in the local or contemporaneous control animals (1/118 = 0.847%) rather than to the almost ten times lower rate of the "expanded" control group discussed in the previous section here (54/60,045 = 0.090%); also, I have assumed all non-control rats to have been exposed at the top level of exposure (7,420 mgm/kgm body-weight) rather than to a series of levels starting at merely 1,000 mgm/kgm body-weight; I have also excluded from consideration the medulloblastoma observed for Animal No. 84-010, but have not excluded the response of any other animal in that study. Each of these features, as mentioned, provides the benefit of doubt to aspartame, i.e., to its "producers" as distinct from its "consumers".

With such additional assumptions, we may tabulate the estimated "virtually safe" levels of aspartame in mgm/kgm body-weight/day for a variety of upper limits on the risk indicated in the column at the extreme left of the table that follows here on the next page.

Note that for each of the two methods of extrapolation, two estimates are given in the table opposite each upper limit on the risk:- one for rats and one for humans. The estimate for the humans is related to the corresponding one for the rats by being 5.23 times smaller than it. This is the factor necessary for "translation" from rats to humans by correcting for the body-area of the two species:- due to its larger size, the human has a body-area per unit mass smaller than does a rat:-

An average male rat in the study considered here weighed 506 Gms., and an average female rat 331 Gms., for a mean weight of 418.5 for the two sexes. Thus a human of average weight of 60 Kgms., sa[illegible] is "worth" on a mass or weight basis 60,000/418.5 = 143.37 rats of average weight. But that same human weighing 60 Kgms is worth on a body-area basis only the two-thirds power of 143.37 i.e., only 27.39 such rats. Thus, to have equivalence for doses expressed in mgms/kgms body-weight between rats and humans, the dosage for the rats must be divided by the one-third power of 143.37, i.e., by 5.23. Hence the factor used in the table that follows.

RESULTS EMANATING FROM THE FORMAL RISK ASSESSMENT INVOLVING BRAIN TUMORS

	"virtually safe" level of aspartame in mgm/kgm bw/day			
	Log-probit method		One Hit method	
Upper limit on risk	for rats	for humans	for rats	for humans
1/100,000,000	0.700	0.134	0.001,278	0.000,244
5/100,000,000	1.349	0.258	0.006,392	0.001,22
1/ 10,000,000	1.809	0.346	0.012,78	0.002,44
5/ 10,000,000	3.674	0.702	0.063,92	0.012,2
1/ 1,000,000	5.050	0.966	0.127,8	0.024,4
5/ 1,000,000	10.95	2.09	0.639,2	0.122
1/ 100,000	15.55	2.97	1.278	0.244
5/ 100,000	36.81	7.04	6.392	1.22
1/ 10,000	54.63	10.45	12.78	2.44
5/ 10,000	146.5	28.01	63.93	12.2
1/ 1,000	232.3	44.42	127.9	24.5
5/ 1,000	759.1	145.2	640.8	123.

It turns out from the entries in the table just above that an ADI of 50 mgm/kgm body-weight for humans is associated by both methods of extrapolation with an upper limit on the risk as high as between 1/1,000 and 5/1,000 population exposed to aspartame to develop brain tumors as a result of exposure to that food additive. For this to actually become evident, it would take many years since such tumors have a very long latent period, i.e., it takes a long time for them to become manifest. Thus, it seems to me that we are dealing here with a huge time bomb.

There is hardly any need for me to emphasize here that this represents an unacceptably high risk or hazard posed by aspartame.

SUMMARY AND CONCLUSIONS.

From what has been discussed in my letter addressed to you last week as well as from what has been presented in the previous pages of this communication, I can conclude the following:-

1. It is impossible for anyone to appreciate just how a determination by the FDA that the G.D. Searle & Co. experimental studies with aspartame were of an unacceptable quality in 1976 can be metamorphosed several years later into a view by that same Agency that essentially the same studies were sufficiently reliable for anyone to assess that this food additive is "reasonably certain" to be safe for consumption by humans.

2. Even if, contrary to the FDA's view in 1976, the quality of the conduct of those studies could be relied upon by the same agency to even begin making such a determination, at least one of those studies had revealed a highly significantly dose-related increase in the incidence of brain tumors as a result of exposure to aspartame.

The full incidence of those brain tumors was not disclosed by G.D. Searle & Co. to the FDA prior to the initial approval for the marketing of aspartame in 1974; moreover, the review of that study in the FDA was so flawed that the Agency apparently did not even realize at that time that only a portion of the observations on brain tumors had in fact been submitted by G.D. Searle & Co. in their petition for that approval.

3. Quite aside from the remarkable significance of the increased incidence with dose of those brain tumors, the ADI of 50 mgm/kgm bodyweight recently set by the FDA for the human consumption of aspartame is alarmingly dangerous in that it involves an extremely high and, therefore, a totally unacceptable upper limit on the risk for those consuming aspartame: between 1/1,000 and 5/1,000 population to develop brain tumors as a result of such exposure.

4. Although in their report the GAO express the view that the FDA "followed its required process in approving aspartame (for marketing)" I would sharply disagree with such evaluation. Although the FDA may have gone through the motions or it may have given the appearance of such a process being in place here, the people of this country expect and require a great deal more from that agency charged with protecting their public health:- in addition to mere façade or window-dressing on the part of the FDA, they require a thorough and scientifically based evaluation by the Agency on the safety of the products it regulates.

Unfortunately this has clearly not been the case here. And without this kind of assurance, any such "process" or dance represents no more than a farce and a mockery of what is truly required.

Sincerely yours

M. Adrian Gross,
Senior Science Advisor,
Benefits and Use Division,
Office of Pesticide Programs

I certify that the signature at left here
is my own and that, to the best of my
knowledge the contents of this letter are
true and accurate.

Sworn and subscribed before me this 2nd
day of November, 1987,

[illegible]
My [illegible] 8-26-91

THE
UNIVERSITY
OF
ILLINOIS
COLLEGE OF MEDICINE
AT CHICAGO

Department of Pediatrics (M/C 856)
840 South Wood Street
Chicago, Illinois 60612 USA

Reuben Matalon, MD, PhD
Professor of Pediatrics
Head, Division of Genetics and Metabolism
Office: (312) 996-5305
Laboratory: (312) 996-5326/5694

Joe J. Hoo, MD
Associate Professor of Pediatrics
Cytogenetic Laboratory
Office: (312) 996-6143
Laboratory: (312) 413-1607

George Hoganson, MD
Assistant Professor of Pediatrics
Molecular Genetics Laboratory
Office and Laboratory: (312) 996-6006

Jar Fee Yung, PhD
Assistant Professor of Pediatrics
Cytogenetic Laboratory
Laboratory: (312) 413-1607

Clinic Appointments:
Henrietta Schotland, MS
(312) 996-7202

Grace Racaza, MSW, ACSW
Social Worker

JoEllyn Taylor, MS
Genetic Counselor

Melody White, MS
Genetic Counselor

October 22, 1987

Mr. James Wagoner
Legislative Assistant
Office of Senator Howard M. Metzenbaum
140 Russell Senate Office Building
Washington, D.C. 20510

RE: STUDIES ON ASPARTAME

Dear Mr. Wagoner:

Aspartame is a synthetic sweetner that contains phenylalanine, aspartic acid and methanol. I have been studying this sweetner in normal individuals and carriers for the disease phenylketonuria (PKU). Individuals who are carriers for PKU cannot metabolize phenylalanine as efficiently as a normal individual. The frequency of carriers for PKU in the U.S. is about 2% of the population and most of these individuals are not aware that they are carriers for PKU.

I have studied 51 individuals (23 carriers and 28 normals) who were given aspartame 100 mg/kg/day for 12 weeks. The results indicated the following:

1) 14% of the normal individuals had blood phenylalanine above 6.0 mg/dl and 5% had levels greater than 10.0 mg/dl (normal blood phenylalanine is 1.0 mg/dl);

2) 35% of the carriers for PKU had blood phenylalanine levels greater than 6.0 mg/dl and 12% had blood levels greater than 10.0 mg/dl;

3) the ratio of blood phenylalanine to tyrosine which should be less than 1.0 was abnormally high in all participants and reached 20.9 in one individual.

Since normal blood phenylalanine level is about 1.0 mg% the data obtained from my study are of concern not only to carriers for PKU but also to normals who are heavy aspartame users. The amount of 100 mg/kg used in this study can be easily attained if one considers a 44 lb child (7-8 years old) who consumes during an entire day 3 cans of soda, 2 cups of jello and 2 milkshakes sweetened with aspartame already reaches 100 mg/kg/day.

At this time when I treat patients with the disease PKU I do not allow their blood phenylalanine to go above 8.0 mg%. A pregnant woman with PKU should not have a blood phenylalanine level exceeding 6 mg%. Therefore, it is not prudent to declare any blood levels of phenylalanine above the physiological norms as harmless. Upsetting the normal ratio of phenylalanine to tyrosine or other essential amino acids is also non-physiological and should not be allowed to happen.

In summary, dammages that can occur from high blood phenylalanine levels are not easy to detect and may take us years to realize their effects on the learning child, the pregnant woman and the population at large. Therefore, I would suggest that intake of aspartame should be allowed only if the physiological levels of blood phenylalanine are maintained. The current allowed daily intake (ADI) of 50 mg/kg/day adopted by the FDA does not address the physiological norms and is not based on any scientific evidence that high levels of blood phenylalanine are harmless.

Sincerely,

Reuben Matalon, M.D., PH.D.
Professor of Pediatrics
Head, Division of Genetics and Metabolism
Director, PKU Clinic

RM:cw

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SCRIPPS INSTITUTION OF OCEANOGRAPHY

LA JOLLA, CALIFORNIA 92093

October 26, 1987

Mr. James Wagoner
Office of Senator Metzenbaum
140 Russell Senate Office
Washington, D.C. 20510

Dear Mr. Wagoner:

I have not really had much time to prepare what I feel would be a good summary of our work on aspartame decomposition. What is enclosed is very brief, but hopefully to the point. If necessary, I can supply a more detailed summary in the future.

Sincerely,

Jeffrey L. Bada

Jeffrey L. Bada
Professor of Marine Chemistry

JLB:lsj
Enc.

Aspartame, a dipeptide containing the amino acids phenylalanine and aspartic acid, is prone to a number of decomposition/alteration reactions. Dominant are cyclization to the cyclic dipeptide or diketopiperazine and stereochemical (racemization) inversion producing the unnatural D-stereoisomers of the amino acids. Attached are diagrams showing these reactions. The rate at which these reactions take place is dependent on the pH and temperature to which aspartame is exposed. In general, under most situations of consumer use of aspartame these reactions occur fairly slowly although data on actual consumer products is meager. In some instances, however, these reactions are very significant, and the reaction products which are produced are not well-studied as far as their nutritional/toxicological properties are concerned. Some examples where these reactions could be significant are in soft drinks exposed to warm temperatures for prolonged periods and in consumer misuse of aspartame such as in cooking or baking.

It is my feeling that consumers should be informed of these possible reactions, and that they are poorly studied from a variety of nutritional, biochemical, and metabolic standpoints.

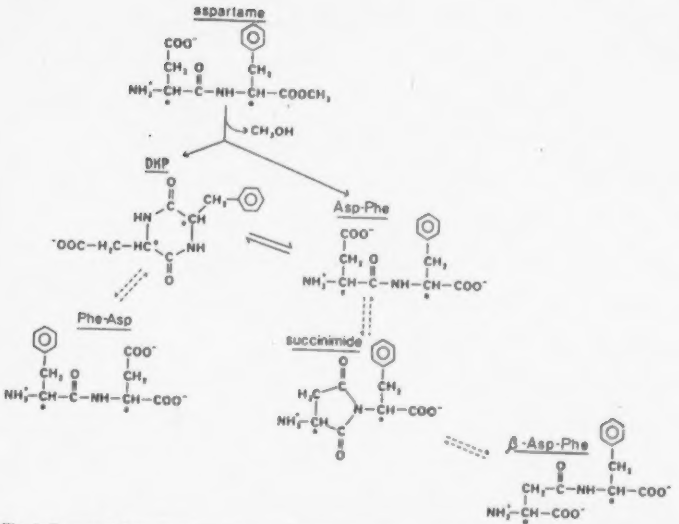
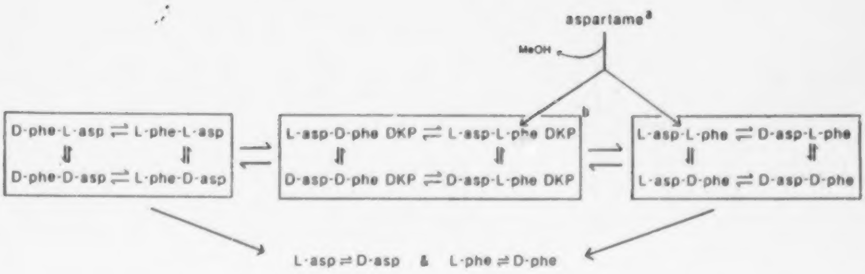


Fig. 1. Proposed decomposition scheme of aspartame showing the various possible products. The symbol • denotes chiral centers so that each of these products may undergo epimerization producing four stereoisomers. Solid arrows represent known decomposition reactions (7–9). Dashed arrows represent possible dipeptide and DKP pathways (11, 17) which may occur during aspartame decomposition.

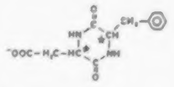
Taken from: S.M. Gaines and J.L. Bada, 1987. Reversed-phase high-performance liquid chromatographic separation of aspartame diastereomeric decomposition products. Journal of Chromatography 389, 219-225.


aspartame[a]
MeOH
b
D-phe-L-asp ⇌ L-phe-L-asp
D-phe-D-asp ⇌ L-phe-D-asp
L-asp-D-phe DKP ⇌ L-asp-L-phe DKP
D-asp-D-phe DKP ⇌ D-asp-L-phe DKP
L-asp-L-phe ⇌ D-asp-L-phe
L-asp-D-phe ⇌ D-asp-D-phe
L-asp ⇌ D-asp & L-phe ⇌ D-phe

Scheme 1. Major decomposition pathways of AP-OMe, and epimerization in the products.

[a] Theoretically, epimerization may occur in aspartame as well as in the dipeptides; internal aminolysis and hydrolysis are so much faster, however, that epimerization in aspartame cannot be detected.

[b] asp-phe DKP =


O
C
HN
CH
CH₂
⁻OOC−H₂C−HC*
NH
C
O

Chiral centers are indicated by *.

Taken from: S.M. Gaines and J.L. Bada, 1987. Aspartame decomposition and epimerization in the diketopiperazine and dipeptide products as a function of pH and temperature. Journal of Organic Chemistry, in press.

UNIVERSITY OF FLORIDA • J. HILLIS MILLER HEALTH CENTER • GAINESVILLE
COLLEGE OF PHARMACY (Box J-487) 32610
DEPARTMENT OF PHARMACODYNAMICS

October 19, 1987

Senator Edward M. Kennedy
Chairman, Senate Committee on
Labor and Human Relations
SD-428
Washington, DC 20510

Dear Senator Kennedy:

I am writing as a concerned scientist in regards to the forthcoming hearings on the safety of aspartame. I have published over 10 scientific papers in refereed journals on the neurotoxic effects monosodium glutamate. Glutamate and aspartate share the ability to activate excitatory amino acid receptors on nerve cells and function normally as neurotransmitters or at excessive extracellular concentrations can cause the death of nerve cells. I wish to address several concerns that I feel are vital to a comprehensive and scientifically sound assessment of the safety of aspartame as an artificial sweetener (food additive).

The specific concerns are as follows:

1. Excitatory amino acids act synergistically to cause both pharmacological and neurotoxic effects. Thus, to consider only aspartame intake in the calculation of risk to neurotoxic damage is completely erroneous. Therefore, daily intake of natural foods high in aspartic and glutamic acid must be considered in addition to foods containing monosodium glutamate (MSG) as an additive. A second point in this regard is the ubiquitous presence of aspartame in the present food supply (children's cereal, soft drinks, snack bars, frozen popsicles, etc). An accurate assessment of total possible intake of aspartame plus other dietary sources of glutamic and aspartic must be made.

2. The correct identification of individuals in special risk groups must be made. Possible candidates at special risk to aspartame include; neonates, the elderly, diabetics, individuals suffering from Chinese-Restaurant-Syndrome and those individuals at risk for cerebral ischemia, epilepsy or neurodegenerative disorders (olivopontocerebellar atrophy, Alzheimer's Disease, Huntington's Disease, etc). Glutamate and aspartate play a pivotal role as neurotransmitters and metabolic disorders involving glutamate or aspartate may be involved in a variety of neurological disorders. Thus, the unregulated dietary intake of excessive amounts of these excitotoxins may exacerbate pre-existing neurological conditions.

EQUAL EMPLOYMENT OPPORTUNITY/AFFIRMATIVE ACTION EMPLOYER

An extensive effort should be made to identify any groups of individuals for which aspartame ingestion would have deleterious consequences. There may also be individuals that show metabolic intolerance to aspartame. This intolerance could be to the aspartic acid as already discussed or to the phenylalanine (such as PKU patients) or methanol. The possibility that aspartic acid and methanol could act synergistically to produce visual disturbances must also be considered (aspartic acid can cause retinal damage and methanol damages the optic nerve). Individuals with defects in key enzymes that inactivate these metabolites of aspartame would be at special risks to various toxic sequelae.

3. A most disturbing action of aspartic acid, given the presence of aspartame in so many products consumed by children, is its ability to stimulate hormone release from the anterior pituitary gland. The aspartic acid analogue, N-methyl-DL-aspartate (NMDA) has been shown to induce large and rapid elevations in plasma levels of luteinizing hormone, follicle stimulating hormone and prolactin. Growth hormone release is also altered by glutamate administration or NMDA infusion. These actions are not toxic in the classical sense but the regulated pulsatile release of anterior pituitary hormones is essential to the normal growth and sexual maturation of children, as well as, the control of the reproductive cycle in mature females. These neuroendocrine effects of a food additive must be considered in regard to the safety of the product. It cannot be emphasized enough that aspartic acid is a neurotransmitter that functions importantly in many complexly integrated physiological processes. Phenylalanine can be converted to tyrosine which serves as a precursor to the catecholamine (dopamine, norepinephrine and epinephrine) neurotransmitters. Thus, even at doses of aspartame that are non-toxic there can be significant pharmacological actions such as disruption of hormone release and changes in brain function.

Specific Recommendations

1. Detailed and comprehensive statistical evaluations of consumer complaints concerning aspartame and disclosure of these findings to the scientific community.

2. Revamped safety testing to include both aged and neonatal rodent and primate testing. The evaluation of both toxic and pharmacological actions of aspartame at levels that approximate total excitotoxin (glutamate and aspartate) intake.

3. An aggressive research program to identify any special groups at risk to aspartame including:

  a. the elderly.
  b. children.
  c. diabetics.
  d. victims of the Chinese-Restaurant-Syndrome.
  e. epileptics.
  f. individuals with cerebral ischemia or hypoxia.
  g. individuals at risk for neurodegenerative disorders.

4. Identification of the incidence of metabolic intolerance to aspartame in the general population. How many people show adverse reactions to aspartame and what is the metabolic basis?

5. Federal funding of research on the neuropharmacological and neuroendocrine actions of long-term aspartame ingestion. Do we have a potential long-term public health concern with unknown actions of chronic daily aspartame ingestion?

6. Public education (warning labels?) concerning the issue of aspartame safety. There is not uniform agreement among the scientific community regarding the safety of either aspartame, saccharin or cyclamates. The public must not assume FDA approval (under duress due to public pressure at the time of approval) assures that a product is biologically innocuous. Future public hearings would certainly be in order.

My concerns are those of a scientist that feels not enough data are available. I do not wish to see consumers as subjects in a large scale clinical trial of a product. I am unable at present to say what the magnitude or scope of any adverse consequences will be to the long-term introduction of aspartame (in combination with MSG) into the food supply. I only hope we have the opportunity to aggressively seek the answers to the issues I have raised using scientific criteria unencumbered by economic, political or bureaucratic artifice.

Sincerely,

Ralph Dawson

Ralph Dawson, Jr., Ph.D.
Assistant Professor

RD/vp

Diplomates in Neurology

NEUROLOGIC ASSOCIATES, p.c.
Gerald A. Schroeter, M. D.
Frederick S. Mortati, M. D.
Howard B. Reiser, M. D.
Lawrence J. Robinson, M. D.

364 E. Main Street
Huntington, NY 11743

Telephone: (516) 271-4040

10 Medical Plaza
Glen Cove, NY 11542

November 2, 1987

Hon. Howard Metzenbaum
Senate Committee on Labor & Human Resources
SR 140
Washington, D.C. 20510

Attn: James Wagoner

Dear Senator:

I have been requested to write you regarding my feelings on NutraSweet, both from the aspect of my clinical experience and clinical opinion regarding such.

It is my feeling, as a neurologist, that NutraSweet-aspartame being a potential neurotoxin may be a factor involved in neurologic symptoms such as headaches, dizzy spells, fainting episodes or convulsive seizures.

My experience with NutraSweet has been inconclusive, with some of my patients reporting adverse reactions such as headaches, dizzy symptoms and convulsive seizures, possibly triggered by or exacerbated by the usage of this product.

I have read several articles on aspartame, including more recent articles alluding to its complete safety, and "no link" between such and convulsive seizures.

It is my recommendation that this product be further scrutinized and evaluated objectively, both clinically and experimentally, so that futher conclusions regarding possible adverse reactions can be ascertained. I will continue to advise my patients with neurologic symptoms to minimize the usage of this product until I am fully convinced of its safety.

Sincerely,

Gerald A. Schroeter, M.D., F.A.A.N.

N.B. Enclosed is a copy of my Curriculum Vitae, as requested.

GAS:cz
cc: Hon. Alphonse D'Amato
Hon. Daniel Patrick Moynihan
Hon. Robert J. Mrazek

CURRICULUM VITAE

Gerald A. Schroeter, M.D.

Clinical Neurologist - Full Time - Neurologic Associates, p.c.

Attending - Medicine/Neurology - The Community Hospital at Glen Cove

Attending - " " Huntington Hospital

Offices: 164 E. Main Street
Huntington, N.Y. 11743

10 Medical Plaza
Glen Cove, N.Y. 11542

Medical Director - Suffolk County Seizure & Neurology Center
(St. Charles Hospital - 1966-73) Retired

Medical Director - Suffolk County M.S. Society

Vice President - Long Island Neuroscience Academy

Chief - EEG Department - The Community Hospital at Glen Cove

Past President - Huntington Hospital Neuro/Neurosurgery Department

Medical Board - The Community Hospital at Glen Cove - 1974-75

Physician Recognition Award - CME - 1979-1982

BSc. - St. John's University - 1957

M.D. - University of Ottawa - 1961

Interne - Stamford Hospital - 1961-62

Residency in Neurology - Bronx V.A. Hospital
Rotating through
Montefiore and Columbia Presbyterian - 1962-65

Diplomate - American Board of Psychiatry & Neurology (N) - 1970

Member - American Academy of Neurology
Suffolk County Medical Society
American Medical Association
Long Island Physicians Association
Eastern Association of EEG

Avoid:/ or Minimize

Nitrate meats (ham, bacon, deli meats)
Pizza
Pickled foods-pickles
Aged cheese (incl. cheddar
Chocolate
Caffeine excess (tea, coffee, colas)
Sour cream - yogurt
Chicken livers
Added salt
Raw onion
Catsup
Red wine/beer
Red wine vinegar
Nuts - peanut butter
MSG excess (Chinese/soy
Avocado, canned figs
Whole wheat
Eggs (OK 2/weekly)
Sulfited white wines
Aspartame - Nutra-Sweet

Perfumes
Toxic
J & J Baby Shampoo & Conditioner (pink)
Suave*, Agree*, Pert*, Finesse*, Silkience*
Body on Tap
Head & Shoulders (white cap)
Prell Conditioner, Breck, Halsa, PermaSoft,
Sassoon, Alberto VO-5, Style I, II, III,
White Rain, Wella Balsam, Clairol Shampoo/Cond.
Most store & generic brands
Scented Hair Sprays & Final Net (unscented)
Scented Mousse

PALM BEACH INSTITUTE FOR MEDICAL RESEARCH, INC.
304 27TH STREET
WEST PALM BEACH, FLORIDA 33407-5299

H. J. ROBERTS, M. D.
MEDICAL DIRECTOR

THE ASPARTAME PROBLEM

STATEMENT FOR SENATE HEARING

NOVEMBER 3, 1987

I am concerned over the escalating number of aspartame-related complaints documented by or reported to interested investigators, the FDA, and consumer groups such as Aspartame Victims And Their Friends and the Community Nutrition Institute.

The most serious reactions I have encountered among 551 aspartame reactors in my nationwide computerized study include severe headaches (45.2%), dizziness (39.4%), decreased vision or blindness (27.9%), epileptic attacks (17.8%), profound confusion and memory loss (28.5%), extreme depression (25.2%), and marked personality changes (16%). Hives, other rashes, itching, mouth reactions, hyperactivity, extreme fatigue, insomnia, menstrual disorders, diarrhea, intense thirst, ringing in the ears, aggravated hypoglycemia, loss of diabetic control, severe weight loss (suggestive of anorexia nervosa), a paradoxic gain of weight, and joint pains also have been prominent. These observations, which have been reported in the references listed, are supported by FDA data.

An unexpected finding has been the occurrence of reactions to aspartame in the relatives (up to 7) of 22 per cent of persons so affected.

The causative or contributory role of aspartame is supported by (1) the gratifying relief or disappearance of these complaints (except for blindness and severe neuropsychiatric features) after its cessation, and (2) their predictable recurrence on rechallenge.

Damage to the retina, optic nerves and brain can be caused by methyl alcohol in heavy consumers. (Aspartame promptly releases 10 per cent methanol by weight when metabolized.) Other complications may reflect the combination of high levels of phenylalanine within the brain, altered neurotransmitter function, severe caloric reduction, and increased release of insulin and other hormones. Recent data also raise the possibility that selective amino acid imbalances of phenylalanine and aspartic acid may accelerate or aggravate Alzheimer's disease, Parkinsonism, behavioral abnormalities, and other neuropsychiatric afflictions.

The problems of aspartame reactions assume even greater importance for certain high-risk groups. They include the many children, pregnant women, older persons, and patients with diabetes, migraine, hypoglycemia, epilepsy, allergies and liver or kidney disease who consume large amounts of such products.

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Severe deficiencies pertaining to the evaluation, licensing, promotion and surveillance of aspartame must be addressed in the face of this potential "recipe for disaster." They encompass (1) the need for accurate clinical data collected by the responsible governmental agencies, including an analysis of tumors (especially brain and urinary bladder) and blood disorders, (2) the arbitrarily high maximum allowable daily intake, (3) the prior resistance by Congress to enactment of legislation that would mandate the proper labeling of aspartame products, (4) the failure to challenge the alleged safety and effectiveness of aspartame in massive promotional campaigns, especially for long-term weight loss, and (5) unfounded bias against saccharin based on limited and controversial studies concerning urinary bladder tumors in male rats.

It is now the burden of regulatory agencies that have minimized or denied the accumulated clinical data to convincingly explain them in terms other than isolated idiosyncratic reactions.

The informational gap caused by the biases and other misgivings of reluctant editors, publishers and chairmen of major medical conferences is a public health and scientific disservice.

Concerning my credentials, I have been certified and recertified by the American Board of Internal Medicine, and am a member of the Senior Active Staff of the Good Samaritan Hospital and St. Mary's Hospital in West Palm Beach. I have authored more than 200 original scientific publications and five texts, and am listed in The Best Doctors In The U.S. and Who's Who In The World.

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H. J. Roberts, M.D.

H. J. Roberts, M.D.

WASHINGTON
UNIVERSITY
SCHOOL OF
MEDICINE
AT WASHINGTON UNIVERSITY MEDICAL CENTER

DEPARTMENT OF PSYCHIATRY

December 8, 1987

Senator Howard M. Metzenbaum
United States Senate
140 Russell Senate Office Building
Washington, D.C. 20510

Dear Senator Metzenbaum:

I have been asked to update the Committee on my position regarding the several neurotoxicology issues that I and other neuroscientists presented before the Public Board of Inquiry (PBOI) on aspartame (Nutrasweet) in 1980. Three separate neurotoxicity issues were focused upon at the PBOI, one pertaining to the neurotoxic properties of aspartate (a major component of the Nutrasweet molecule), another to the neurotoxic properties of phenylalanine (the other major component of the Nutrasweet molecule) and the third to brain tumors. I will discuss the status of each issue as I see it today.

1. Aspartate neurotoxicity.

Aspartate (Asp) and the related compound, glutamate (Glu), are present in high concentration in the brain where they serve as excitatory neurotransmitters and participate in much of the information processing that occurs in the mammalian central nervous system. Paradoxically, these substances have striking neurotoxic potential--if allowed to have sustained contact with receptors on the exterior surface of the nerve cell, they literally excite the cell to death. The reason they do not manifest neurotoxic activity under ordinary circumstances is that they are synthesized and contained inside the nerve cells and are emitted outside only in tiny amounts for transmitter purposes; after transmitting a signal (exciting a neighbor cell), they are immediately (within milliseconds) taken back up into the cell.

Eighteen years ago, before the above information was known, my research group discovered that when Glu or Asp are administered orally to animals of various species including monkeys, they destroy nerve cells in certain parts of the brain. We found that Glu and Asp act in concert such that when ingested together they add to one anothers toxicity. Although we found animals at any age susceptible to Glu/Asp neurotoxicity, immature animals were much more sensitive than adults. Over the years neuroscientists have developed a much better understanding of this neurotoxic phenomenon. When Glu or Asp are ingested, they are absorbed into the blood very rapidly which causes blood

Phone: (314) 362-7007
4940 Audubon Avenue
St. Louis, Missouri 63110
(Medical School Box 8134)

levels of these amino acids to be transiently elevated. This, poses no hazard for most portions of the brain because Glu and Asp are prevented by blood brain-barriers from entering most regions of the brain. However, there are several small regions of brain that lack blood brain barriers, and blood-borne Glu and Asp freely penetrate these brain regions. This brings Glu and Asp in direct contact with receptors on the exterior surfaces of nerve cells and places such nerve cells in jeopardy of being excited to death. Nerve cells in immature brain are at greatest risk of being destroyed because important protective mechanisms are not yet functionally competent. In the neuroscience community today, this is commonly referred to as excitotoxic cell death and Glu and Asp are known as excitotoxins. The Glu and Asp contained in the brain are called endogenous excitotoxins and the Glu and Asp encountered in the environment are called exogenous excitotoxins.

The major source of human contact with exogenous excitotoxins is through the commercial food supply. Glu, in the form of its sodium salt, monosodium glutamate (MSG), is a very heavily used food additive. In 1969 when I first described the extreme sensitivity of the immature brain to the toxic effect of Glu, baby food manufacturers were adding very large amounts of Glu to baby foods. After I presented my research findings in testimony before the Senate Select Committee on Nutrition and Human Needs (1970), the Nixon white house worked out an agreement between FDA and the industries concerned whereby baby food manufacturers (who comprised a small fraction of the Glu market) would "voluntarily" quit adding Glu to baby foods. I applauded this part of the agreement but not the accompanying quid pro quo which was that FDA would continue to classify Glu as GRAS (generally regarded as safe) and would continue to allow other food manufacturers (comprising the bulk of the Glu market) to add unlimited amounts of Glu to "adult" foods destined to be ingested by consumers of all ages. Thus, Glu was taken out of baby foods but was not taken out of foods fed to babies. And, to this day, FDA still classifies Glu as GRAS, thereby conveying the dangerous message to parents that it is perfectly safe to feed Glu to babies.

Another major source of Glu and Asp in foods is hydrolysed vegetable protein (HVP). HVP is a mixture of Glu, Asp and other amino acids. It is because of its exceedingly high Glu concentration that HVP is used as a food flavoring agent. After the baby food industry quit adding Glu to baby foods in 1970, they immediately began adding HVP in huge amounts in order to bring the Glu level (i.e., the flavor level) back to where it had been before. Throughout the 1970's I wrote letters, testified at hearings, etc. trying to get the baby food companies to quit adding HVP to baby foods and trying to get FDA to take a more responsible position. In the late 1970's, the baby food industry finally decided that their subterfuge was working more against them than for them so they opted for a clean image and quit adding excitotoxins to baby foods. No headway was made with FDA; the agency is still misleading and miseducating mothers into thinking that it is perfectly safe to feed Glu, HVP or any other excitotoxins to babies.

When Nutrasweet was first proposed as a sweetener, I was concerned because 50% of the Nutrasweet molecule is Asp and they were proposing to add it primarily to childrens foods and beverages (kool aid, coated breakfast cereal, etc.). In 1974, FDA approved Nutrasweet for such uses without even requiring the manufacturer to determine whether it has the kind of neurotoxicity that Asp was known to have. Therefore, I obtained some Nutrasweet in 1974, administered it orally to infant mice and demonstrated that it destroys nerve cells just like Glu and Asp do. I sent this evidence to FDA and filed a formal protest against their approval of the additive. Because of information that was surfacing at that time implicating the manufacturer in apparent fraudulent practices, FDA stayed their approval of Nutrasweet and granted me the right to a hearing which was to take place after FDA completed their investigation of the manufacturer. The hearing finally took place in 1980 as a PBOI. In framing the issues for the PBOI, I insisted that the issue of Asp neurotoxicity not be considered in the narrow context of Asp alone but rather in the context of adding Asp to a food supply that already contains a similar excitotoxin (Glu) in amounts potentially dangerous for immature consumers.

In 1979 the Commissioner of FDA (Acting Commissioner, Sherwin Gardner) selected a 3 member panel of scientists to serve as judges for the PBOI. I strongly opposed the appointment of one of these judges on grounds of conflict of interest and lack of qualifications. The Commissioner arbitrarily overruled my objections allowing me no alternative but to participate in the PBOI under protest. As it turned out, the panel member whom I considered inappropriate was given a disproportionately large share of responsibility for deciding the Asp issue. The other 2 judges focused primarily on the brain tumor issue which they considered of overriding importance because it provided ample basis in itself for recommending disapproval of the additive. The result of this "division of labor" arrangement was that although all 3 judges signed the report, a single inappropriate judge decided that the Asp component of Nutrasweet did not pose any safety hazard. He based his decision on a consideration of Asp alone without regard to the real issue, i.e., is it safe to add Asp to the large amounts of Glu that are already adulterating the food supply?

My opinion regarding the status of the Asp neurotoxicity issue is that it was handled in an inappropriate manner by the PBOI panel; the real safety issue still remains unresolved and human young are being exposed to potentially dangerous and ever increasing amounts of Glu and Asp, both of which are exogenous excitotoxins that can rapidly destroy nerve cells in the developing brain. The amount of Glu being added to foods today is dangerous in itself; adding a second excitotoxin (Asp) to the same food supply increases the danger.

To put the issue in proper perspective, let me bring you up to date on other developments in the field of excitotoxicology. It is now becoming abundantly clear that endogenous excitotoxins (i.e., the Glu and Asp naturally present in the brain) are responsible for several very common types of brain damage that afflict humans--for example, the brain damage that is associated with stroke, cardiac arrest and perinatal asphyxia (cerebral palsy). In these conditions there is a sudden release of Glu and Asp from cells in the brain coupled with paralysis of the mechanism for taking them back into the cell. If Glu and Asp are released from cells and not rapidly taken back up, they flood the excitatory receptors on the external surface of nerve cells and excite nerve cells to death. It has recently been shown that certain drugs which block the action of Glu and Asp at these excitatory receptors can protect the animal brain against damage associated with stroke, cardiac arrest or perinatal asphyxia. Thus, it is an ironic fact that today knowledgeable neuroscientists in many parts of the world are working fervently to develop methods for preventing endogenous excitotoxins from damaging the human brain, while other elements of society, including the FDA, are promoting and sanctioning the adulteration of foods with unlimited amounts of exogenous excitotoxins which are known to destroy nerve cells in the mammalian brain following oral intake.

2. Phenylalanine Neurotoxicity

I understand that the phenylalanine neurotoxicity issue is the major focus of the present hearings and that it is being addressed by other scientists. Therefore, I will just state my position without much explanatory background.

At the PBOI I argued that Nutrasweet would unnecessarily complicate and undermine the therapy of children who are homozygous for PKU and who must adhere to a low phenylalanine diet; for the parents of these children and their doctors, Nutrasweet is, at best, an enormous nuisance. I also pointed out that the screening programs which attempt to detect homozygous PKU victims at birth are not overly effective, there being approximately 30 % of such victims who escape detection. My opponents acknowledged this but argued that Nutrasweet would not contribute to the mental maldevelopment of these children because this maldevelopment already has irreversibly occurred before the child would be old enough to come in contact with Nutrasweet. I countered with the observation that babies can be seen all over the United States, even in pediatric hospital wards, sucking on baby bottles containing Kool Aid. This point was ignored, as were other relevant points I presented on the phenylalanine neurotoxicity issue.

I raised a very important issue concerning a small but not insignificant population of individuals (several thousand) who are called PKU variants. These people are found at birth to have a PKU-like defect but it is not severe enough to warrant the diagnosis of PKU, so the child is not stigmatized with the PKU diagnosis and is not placed on a low phenylalanine diet. When female PKU variants reach child bearing age, and become pregnant, they will not take special precautions to avoid Nutrasweet because they do not know they have a PKU-like illness. If such a person follows a normal diet during pregnancy, her blood phenylalanine levels will be high because of the partial PKU-like defect and her fetus will be exposed to even higher phenylalanine levels because phenylalanine blood levels are increased (approximately doubled) when phenylalanine is transfered across the placenta from the maternal to the fetal circulation. Thus, even on a normal diet this mother will be exposing her fetus to amounts of phenylalanine that are approaching the toxic threshold, i.e., the threshold for causing mental retardation. All it would take to exceed the toxic threshold and assure that the fetus will be born severely retarded is for the mother to use Nutrasweet during pregnancy (hoping to avoid excessive weight gain). This is a clear cut example of mental retardation that could be anticipated and prevented by an enlightened regulatory establishment. Thus far, FDA has dealt with this problem by simply ignoring it.

It is also an exceedingly important question, but one that is more difficult to assess, whether Nutrasweet use during pregnancy by a person who is heterozygous for PKU might cause her fetus to be born less intelligent than otherwise might have been the case. This is an important issue because there are many PKU heterozygotes in the world who are unaware that they have the PKU trait. I trust others who are testifying at your hearings will address this issue.

Finally, there is another important point that was raised at the PBOI which may be relevant to the types of Nutrasweet-related consumer complaints that have been heard subsequently. Contrary to the claims of Nutrasweet proponents, ingesting phenylalanine as part of the Nutrasweet molecule is not the same as ingesting phenylalnine as part of a food protein molecule. There are several complex mechanisms that cause more phenylalanine to end up in the brain after Nutrasweet ingestion than would occur from ingesting the same amount of phenylalanine contained in food protein. Thus, humans who ingest large amounts of Nutrasweet are likely to have significant increases in brain concentrations of phenylalanine. Since phenylalanine feeds into important metabolic pathways which regulate the levels of several neurotransmitters in the brain, it is reasonable to expect that ingesting large amounts of Nutrasweet might have effects on the central nervous system. Incidentally, the vast majority of Nutrasweet consumer complaints that have come to my attention do pertain to the central nervous system. I doubt whether the thousands of lay citizens who have generated these complaints have thought it out ahead of time and conspired to make all of their complaints sound like their central nervous system is being affected. It should also be mentioned that effects such as menstrual difficulties are correctly interpreted as disturbances of the central nervous system since various Asp or phenylalanine-related neurotransmitters in the brain regulate the amount of pituitary hormones that circulate in the blood and control menstrual functions.

The fact that consumers have frequently complained of seizures in association with Nutrasweet ingestion warrants special attention. This was not a type of side effect that was anticipated or discussed at the PBOI. However, in retrospect it should have been. It is known from the PKU literature that, in addition to mental retardation, nearly 80% of untreated PKU patients have electroencephalographic evidence suggestive of epilepsy and over 30% have frank epilepsy. Placing such individuals on a low phenylalanine diet does not reverse the mental retardation but it does ameliorate the manifestations of epilepsy. This suggests that influx of excess phenylalanine into the brain can make a person seizure-prone for as long as the influx continues. Thus, there is medical precedent for expecting that consumers might experience seizures in association with Nutrasweet ingestion.

3. Brain Tumors

This is an exceedingly complex topic which, unfortunately, has a history riddled with appearances of fraudulant practices by the manufacturer of Nutrasweet and ineptitude and/or malfeasance on the part of FDA officials. In the mid 1970's, when I reviewed the Nutrasweet record in preparation for the hearing I had been promised, I came upon a peculiar study which the manufacturer had submitted to FDA and which FDA had unquestioningly accepted as evidence for the safety of Nutrasweet. The study showed that in 320 Nutrasweet-fed rats there were 12 brain tumors whereas in a group of concurrent control rats which were not exposed to Nutrasweet, there were no brain tumors. Being a neuropathologist, I know that spontaneous brain tumors in laboratory rats are extremely rare. The archival literature documents an incidence not exceeding 0.6%. Since the above incidence in Nutrasweet-fed rats is 3.75%, this suggests that Nutrasweet may cause brain tumors and certainly suggests the need for additional in depth research to rule out that possibility.

The manufacturer had done an additional study and submitted it to FDA at the same time as the former study was submitted. The second study also showed a very high incidence of brain tumors in Nutrasweet-fed rats but in this study the control rats also had a similarly high incidence. This did not make any sense, unless both the control and experimental rats were exposed to a tumor promoting agent. A subsequent FDA investigation of the laboratories where these studies were conducted revealed appearances that the control and experimental animals may very well have been fed one another's chow in a sloppily randomized manner so that, in essence, all animals on the study may have been fed Nutrasweet during portions of the study. The judges at the PBOI agreed with me that the exceedingly high incidence of brain tumors in the Nutrasweet-fed rats of the first study and a similarly high incidence in all rats of the second study was a "bizarre" collection of data that could not be considered evidence for the safety of Nutrasweet.

There were other problematic aspects of the brain tumor data. In the pre-1975 records that I reviewed, it was clear that several competent pathologists had carefully examined the original microscopic slides from the first study and agreed that there were 12 brain tumors in the Nutrasweet-fed rats and zero brain tumors in the controls. When the FDA conducted a task force investigation of these laboratories in 1975, they singled out these studies for further investigation and ordered that all laboratory records, including microscopic slides etc. be impounded under FDA seal. Several years later when a group of pathologists (EUREP) was sent to authenticate these studies, they could not find the microscopic slides. The EUREP pathologists were finally taken to a laboratory where the slides were not supposed to be and there they found some but not all of the original slides. Clearly they had not been kept under FDA seal and by mysterious coincidence the slides that were finally presented to the EUREP pathologists contained evidence for 11 brain tumors in Nutrasweet-fed rats and 1 tumor in controls. It is important to recognize that if there are zero tumors in the controls, it is very difficult to argue that the tumor incidence in the control and Nutrasweet-fed rats is the same. But if there is 1 tumor in the control group, it is possible with statistical acrobatics to reach the conclusion that the incidence is the same. And, indeed, this is exactly the argument that the manufacturer and FDA Bureau of Foods pressed at the PBOI. They accepted the finding of 1 brain tumor among the controls even though the authentic record showed zero brain tumors in controls, then they proceeded to break down the animals into smaller and smaller sub groups according to sex, dose level etc and finally the 1 brain tumor in one sub group of control animals appeared to be not significantly different from 2 or 3 tumors in each of the experimental sub groups. I seriously doubt whether this method of data analysis would stand the scrutiny of competent disinterested statisticians. Even more seriously I wonder why FDA allows microscopic slides to disappear (while supposedly impounded) and why they do not question the de novo emergence of a brain tumor among the controls when the slides reappear.

The PBOI panel member who was primarily responsible for reviewing the brain tumor issue was Peter Lampert, M.D., Neuropathologist and chairman of the pathology department at Univ. of Calif. San Diego. Dr. Lampert personally examined the microscopic slides pertaining to the brain tumor studies and told me a year or so after the PBOI report was completed that he had been surprised at the large size of the brain tumors in the Nutrasweet-fed rats. This reinforced his impression that they had been caused by some tumorigenic agent since spontaneous brain tumors are not only rare in laboratory rats but when they do occur they are usually not so large. Dr. Lampert is now deceased; he died in 1986 of cancer. At the time he participated in the PBOI, he was the President of the American Association of Neuropathologists. I had nominated him to serve on the PBOI panel.

If Nutrasweet is a tumorigenic agent, one possible mechanism would be that its breakdown product (DKP) might be responsible. Therefore it is very important that the DKP breakdown product be studied separately to rule out any tumorigenic potential. This is particularly important if Nutrasweet is to be used in beverages since it breaks down much more readily in beverages. The manufacturer did conduct one study purporting to show that DKP has no tumorigenic potential but this was also a study riddled with appearances of fraud and/or incredibly sloppy and unreliable laboratory practices. In 1977, FDA sent a field team to investigate the manufacturer's laboratory where this study was conducted and they found evidence suggesting that the rats in the DKP study may not have actually been fed much if any DKP. The records suggested that the feed had been offered to the rats in powered form with the DKP added in large chunks. Rats are smart enough to push aside the chunks of DKP and eat the powered chow. Remarkably, one of the research technicians who worked on that study photographed a sample of the feed to show how large the DKP chunks were and she left the photograph in her record book. Another person employed in the laboratory at the time was known to have been concerned that the feed was not being properly mixed. That person had moved to a new job with another manufacturing firm. The FDA inspectors called him at the new site and he volunteered information by phone that he did remember the DKP study and did believe the DKP chunks were large enough that the rats could select the chow and avoid the DKP. Then the inspectors went to the new job site to formally interview him and they noticed that someone from G.D. Searle had signed in immediately before them. When they reached the interviewee, he was unwilling to talk to them. When they tried to interview an individual who had been director of the laboratory in which that study was performed, he declined to talk to them on advice from his lawyer. When they interviewed the individual who mixed the feed for the DKP study over a two year period of time, he could not remember anything about the study. This information was sent as a field inspection report to the FDA Bureau of Foods where it was buried. The inspection team had not proven that the feed sample in the photograph was definitely the feed fed to the animals so Bureau of Foods concluded that there was no evidence of wrong doing. Also they concluded that this DKP study adequately proved that DKP has no tumorigenic effects.

I am intimately familiar with the details of the above circus performance because, although the FDA field inspection had been done secretly and FDA intended for the field inspection report to remain secret, I was informed by a prior FDA official that the inspection had taken place and was advised to seek the report through freedom of information channels. It was difficult to obtain, and at one point they flatly refused to supply me with a copy of the photograph of chunky feed claiming that it was property of the manufacturer. However, finally I did get the full report and a copy of the photograph. At the PBOI neither G.D. Searle nor FDA Bureau of Foods volunteered any information about the field inspection although both of them, as participants in the PBOI, were bound by FDA rules to provide the PBOI record with all information relevant to the safety of Nutrasweet. Since they were not forthcoming with this information, I asked for permission to introduce it at the time of the PBOI. The PBOI judges listened to a brief preliminary presentation then interrupted me saying that they needed to have an intermission. They returned from the intermission and said that they would not attempt to evaluate this information but suggested that I might want to air it before some other type of tribunal.

As you know, the PBOI judges unanimously recommended that Nutrasweet not be approved. However, the Commissioner of FDA arbitrarily swept aside the PBOI recommendations and summarily approved Nutrasweet for various foods, then a year or so later for the beverage industry and now I understand the agency intends to approve it for baked goods (it also breaks down rapidly when heated). In his written decision approving Nutrasweet, the Commissioner of FDA argued quite incorrectly that the spontaneous incidence of brain tumors in Sprague Dawley rats is much higher than 0.6%. In spurious support of this conclusion he cited several irrelevant and/or unreliable studies which he considered more compelling than the appropriate scientific evidence cited by the PBOI judges. Also, he biased his analysis of the brain tumor data by assuming the presence of a primary brain tumor in the control rats even though the authentic record showed no such tumor.

Although there is one study that has been reported since the PBOI which claims to have demonstrated that neither Nutrasweet nor DKP has tumorigenic activity, I am not very impressed with this study. It was conducted by the Ajinomoto Co. of Japan which is one of the world's largest manufacturers of Monosodium glutamate and hydrolyzed vegetable protein and a company which I believe has had a contractual relationship with GD Searle to manufacture Nutrasweet. This study, which was reported sketchily in a journal of poor quality, pertains to a different strain of rat than was used in the GD Searle studies (Wistar instead of Sprague Dawley) and therefore has not adequately addressed the questions raised by the GD Searle studies. The only way to address those questions is to conduct studies that use the same strain of rat and carefully control all experimental variables which were not carefully controlled in the GD Searle studies. One wants to know why Sprague Dawley rats exposed to Nutrasweet had a 3.75% incidence of brain tumors in the GD Searle study. Would another study of Sprague Dawley rats, if properly conducted, show the same thing or would it cleanse the record and show that there is a very low incidence of brain tumors in both the Nutrasweet-fed and control rats? The record has not been set straight by the Ajinomoto study on Wistar rats briefly reported in a journal which is not rigorously refereed (and whose editor is financially dependent on the food industry). The FDA Commissioner's office stated at the time he approved Nutrasweet that he was not relying on the newly reported Ajinomoto study but rather was satisfied with the original GD Searle data on Nutrasweet and did not believe any further studies are necessary. I am not satisfied with the original GD Searle studies. The record shows them to be of exceedingly poor quality and the only way to overcome such a record is to have the key studies repeated, preferably by an independent laboratory of the highest possibly integrity.

Sincerely,

John W Olney

John W. Olney, M.D.
Professor of Psychiatry and Neuropathology

JWO:vt

July 1987 - Scientific American

SCIENCE AND THE CITIZEN

Sweet Talk

Since its introduction in 1981 the artificial sweetener aspartame, sold as NutraSweet, has soared in popularity; it has taken the place of sugar in so many diet drinks and foods that by 1985 its annual U.S. consumption exceeded 3,500 tons. Yet recent experiments are re-igniting concerns expressed at the time of introduction that aspartame may affect brain chemistry, even when it is consumed in near-normal amounts. Several laboratories have evidence suggesting that large but not abnormal doses cause behavioral changes in human beings. Clinical investigators presented the new results to industry executives and Federal Government officials at an informal meeting in Washington in May.

One investigator, Paul Spiers of Beth Israel Hospital in Boston, gave preliminary results indicating that normal volunteers on a high-aspartame diet (equivalent to the amount of aspartame in about 12 cans of diet soda consumed in 24 hours by someone weighing 110 pounds) do worse than matched controls on standard tests of higher brain function; their performance (unlike that of the controls) got worse on successive tests. Subjects also complained more of headaches and dizziness when they took aspartame.

The effects are thought to be due to phenylalanine, an amino acid that is one of aspartame's three constituents. (It is also sold as a dietary supplement in "health food" stores.) Phenylalanine is a component of all protein, but brain levels are higher when it is taken in aspertame rather than in proteins, whose other amino acids impede its uptake. Phenylalanine has chronic neurotoxic effects: phenylketonuria, a disease of infancy that causes mental retardation and seizures if it is not treated, results from inherited defects in the enzyme phenylalanine hydroxylase. What is more, a number of healthy people—as many as one in 50 or 70—fail to metabolize phenylalanine efficiently because they have only a single adequate copy of the phenylalanine hydroxylase gene rather than the normal two copies. Blood phenylalanine levels of such individuals have been shown to reach peaks higher than is normal for a given dose.

Spiers's experiments used the dosage of aspartame (50 milligrams per kilogram of body weight per day) that is the "acceptable daily intake" established by the Food and Drug Administration. Results presented by Louis J. Elsas of the Emory University School of Medicine indicate that in individuals who have only one effective phenylalanine hydroxylase gene, phenylalanine slows brain waves at a dosage equivalent to only 34 milligrams per kilogram per day of aspartame. A can of diet soda typically contains about 200 milligrams of aspartame. According to Reuben K. Matalon of the University of Illinois College of Medicine in Chicago, doses of from 50 to 100 milligrams per kilogram per day of aspartame may be "not that uncommon." He found that when the higher dose is continued over a period of weeks, the phenylalanine level in 14 percent of normal subjects and in 35 percent of those who have only one functional gene exceeds the level considered to be excessive for pregnant women.

Commenting on the newly presented findings, a NutraSweet Company scientist stresses that the data are "preliminary." More specifically, he maintains that Matalon's study lacked a control group. Matalon counters that he has plenty of control data from earlier studies. The NutraSweet spokesman also points out that the Elsas study revealing changes in brain waves failed to detect behavioral effects of the kind reported by Spiers.

A possible explanation for any behavioral effects is suggested by experimental-animal results reported at the meeting by Matthew J. During of the Massachusetts Institute of Technology. In rats, he said, high doses of phenylalanine inhibit synthesis of the neurotransmitter dopamine. Several laboratories have found that high doses of aspartame can increase the frequency of seizures or lower the stimulation necessary to induce them in laboratory animals, although there is no evidence that it actually causes seizures.

The Food and Drug Administration's original approval of aspartame in 1981 was criticized because some scientists in the agency had reservations about the test data submitted by the then manufacturer, G. D. Searle & Co., but a subsequent independent review approved the FDA's decision. Searle says that no food additive has had as intense an evaluation as the one undergone by aspartame.

Richard J. Wurtman of M.I.T., the conference organizer, points out that because aspartame is classed as a food additive rather than a drug, adverse reactions do not have to be reported to any Government agency and continuing safety monitoring is not required by law. New legislation is expected to be proposed soon. -Tim Beardsley

Expert Still Troubled by Aspartame

Safety of NutraSweet for Children, Pregnant Women Disputed

PEPSI LIGHT
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Chew-On

By David Zimmer

Aspartame, the low-calorie sugar substitute marketed as NutraSweet, is one of the amazing success stories of the 1980s. In the four years since the artificial sweetener found its way onto grocery store shelves, more than 100 million Americans have tried it. They have tasted it in more than 90 types of products ranging from diet soft drinks to sugar-free gum. Last year, its manufacturer, G.D. Searle & Co., reported sales soaring to $535 million. By 1986, some expect it to top $1 billion.

But there is a possible dark side to all this. Aspartame contains a potentially harmful component, an amino acid called phenylalanine. Too much of it can cause brain damage, especially in fetuses and newborn of genetically susceptible women, according to studies done by Dr. Louis Elsas of Emory University in Atlanta.

"The big unanswered question," said Elsas, "is if pregnant women taking artificial sweeteners can elevate their blood level of phenylalanine to concentrations that adversely affect their fetuses. Is the damage from phenylalanine produced by a threshold effect? Or do little bits of the problem occur at lower levels?

"Aspartame is being promoted as something good for you. But I don't think that it is a legitimate thing for our nation to be exposed to in large quantity."

Searle said reports about potential adverse effects of aspartame on pregnant women and infants were "misleading and do a disservice to consumers." The Chicago-based firm pointed out that in 1981, the Food and Drug Administration found the product to be safe and effective.

Searle does not dispute the contention that high levels of phenylalanine can cause damage in fetuses. But it says there is no cause for alarm because current consumption amounts are not even close to a point where they might pose a problem. Most important, it says that studies on pregnant animals show that even at "abuse levels," aspartame presents no hazard to the fetus.

Nonetheless, Elsas, director of medical genetics at the Atlanta school, said he is concerned, in part, because the sweetener's sale has been so [illegible] and there are still some unknowns about the product. What worries him—and this is not based on any study but his own personal thoughts as a scientist—is the notion that aspartame's effects could be slow and subtle. They could take a generation or more to uncover.

"It's not going to be as overt as explosion," Elsas said recently on "Nightline," an ABC-TV news program. "We may not be able to see the effects for a generation. And then we'll suddenly see a lot of kids with behavioral abnormalities—with IQs that aren't reaching what . . . we anticipated from their educational or their genetic input."

Searle says that more than 20 years of testing in animals has shown aspartame to be safe over long periods. Elsas acknowledges there has been no documented negative side effects of aspartame. Nor has he personally conducted a study on the sweetener.

But he has done research with children and young adults with gene defects who ingested phenylalanine at high levels and found that their reaction time had slowed. That means phenylalanine can produce quantifiable changes in brain function. "I believe," he says, "the unlimited use of phenylalanine products should be moderated especially in certain groups."

A pediatrician and a biochemist, Elsas is focusing on patients with a rare genetic disorder called phenylketonuria or PKU. These individuals cannot metabolize foods containing phenylalanine. As a result, the chemical concentrates in their brains. This can cause retardation in fetuses and newborns who have this genetic disorder. Many states require tests to discover PKU babies who must then be kept on special diets.

Elsas is also concerned about parents of these children, who are normal but may carry one of the two genes needed to have PKU. "There is a genetically susceptible subpopulation of well over a million women whose fetuses may be at risk if they take indiscriminate amounts of phenylalanine," says Elsas. They, too, he says, may also have an impaired ability to metabolize phenylalanine.

Since it is not always possible to detect these single gene carriers before a PKU baby is born, the vast majority don't know who they are. About 1 percent of babies delivered each year are born to mothers who are PKU carriers.

People in whom high levels of phenylalanine may pose problems, Elsas said, are:

- *Pregnant women.* If blood phenylalanine rises to a level high enough to cause problems, the child's brain development could be affected.
- *Children under 6 months.* A high level of blood phenylalanine can produce irreversible brain damage by slowing formation of mature brain cells and by altering the formation of myelin cells that insulate parts of the brain.
- *Older children and adults carrying the PKU disorder.* A high blood concentration of phenylalanine will reduce the brain's ability to function as quickly and efficiently. But these changes are reversible once the level of phenylalanine returns to normal.

The flaw in Elsas' argument, says Daniel Azarnoff, president of research and development for Searle, is that he has no idea what is a dangerous level of phenylalanine concentration. Moreover, he said, Elsas' concern that people may be getting toxic amounts of phenylalanine flies in the face of scientific data. "He is saying people eat a lot of aspartame," says Azarnoff. "The evidence is they don't."

> *"I don't think that it is a legitimate thing for our nation to be exposed to in large quantity."*
>
> — aspartame researcher Dr. Louis Elsas

The FDA has set 50 milligrams of aspartame per kilogram (2.2 pounds) of body weight as an acceptable daily intake. To reach that amount, Searle says, a 132-pound person would have to drink 18 cans of diet soda in a day. The average 12 oz. can of diet soda contains 170 milligrams of aspartame, Searle says.

But Dr. William Patridge of the University of California at Los Angeles says the FDA has underestimated consumption of aspartame. Patridge could not be reached for comment. However, the magazine Common Cause said Patridge wrote to the FDA in 1983 citing figures showing how children eating aspartame-sweetened foods all day could be on their way to consuming the maximum amounts the FDA uses for its safety assessment.

Searle says that tests it sponsored show no harmful effects have been seen even at levels of 200 milligrams—four times the FDA's intake standard. However, the quality of Searle-sponsored studies has been criticized. Sen. Howard Metzenbaum (D-Ohio) has complained that the FDA overruled many scientific questions raised about the reliability of testing. A federal investigation is now under way.

Elsas also argues that the FDA's own publications show that the daily phenylalanine intake of some children ages 7 to 9 goes as high as 70 milligrams per kilogram of body weight—exceeding the agency's acceptable daily amount of 50 milligrams. What Searle's studies do not show, he says, is long-term effects at intermediate levels. In addition, one scientist, Richard Wurtman of the Massachusetts Institute of Technology, says some foods intensify the effects of phenylalanine. "If one drinks a beverage containing aspartame at the same time one eats a carbohydrate-rich food," Wurtman says, "then aspartame's effect on brain phenylalanine is doubled."

To try to clarify the situation, Dr. Reuven Matalon of the University of Illinois has started a study funded by the National Institutes of Health to look at the effects of aspartame on PKU carriers as well as on normal individuals. The study will take about two years.

"In the meantime, I don't think it is fair to express concerns about aspartame as conclusions," he said. "There is no data to implicate it in any difficulty. At the same time, we do not know what a high level of intake will do and where the danger point comes. Until we get the data, if I were the FDA, I would recommend that pregnant women use caution. Moderation should be the key." ■

HEARING ON NUTRASWEET
by the
SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

STATEMENT BY JANET SMITH
EXECUTIVE DIRECTOR
ASPARTAME CONSUMER SAFETY NETWORK

The Aspartame Consumer Safety Network (ACSN) is a coalition of consumer groups* that are working to inform the American public of the serious adverse health effects that many consumers believe they have experienced as the result of consuming products containing NutraSweet. The unresponsiveness of the federal Food and Drug Administration and the manufacturer of NutraSweet to these health concerns is the primary reason for the establishment of ACSN.

Thousands of individuals across the country have contacted our member organizations, concerned about a wide range of neurological symptoms that they have associated with NutraSweet. Reported symptoms include seizures, convulsions, depression and other behavioral changes, memory loss, dizziness, chronic, debilitating migraine headaches, blindness and other vision impairments, and hearing loss. These are the same kinds of symptoms reported to the FDA by over 4,000 consumers, the largest number of complaints about a food additive ever filed with that agency.

This is occuring at the same time that a growing number of prominent scientists including Dr. Richard Wurtman of MIT, Dr. William Pardridge of UCLA, and Louis Elsas of Emory University Medical Center are raising questions about the safety of this product. Increasingly, physicians--particularly neurologists and obstetricians-- are recommending that their patients refrain from consuming products containing NutraSweet.

Responses by the FDA to individual concerns expressed by inquiring consumers have varied widely. In the Dallas Region, many consumers have been told that no safety concerns exists (see attached letter from Mary Stoddard). Others have been referred to an AIDS Hotline for further information! Individual written responoses from the FDA to consumers state that no scientific research has been conducted which raises any questions of safety (see attached letter to Lynette Bailey).

These responses are not only misleading to the individual consumers who are concerned about their health. Such

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Aspartame Victims and Their Friends, the Community Nutrition Institute, and local groups have together organized the Aspartame Consumer Safety Network.

irresponsible responses may be needlessly extending the pain and suffering of individuals whose adverse health effects could easily be relieved or eliminated by simply removing NutraSweet from their diets.

In short, the Aspartame Consumer Safety Network believes that ample evidence exists that the public safety is being jeopardized through the current marketing of NutraSweet and that immediate steps should be taken to protect the health of American consumers through the immediate implementation of a series of protective measures. Specifically, we urge the following measures be taken:

1. Strengthen product labeling requirements. Too many consumers who seek to avoid or limit product intake cannot currently do so because not all products containing NutraSweet are so labeled, or because of other inadequate information. Labels should identify the amount of NutraSweet contained in every NutraSweet product; possible hazards associated with the heating of NutraSweet; Acceptable Daily Intake levels; and the symptoms that have been associated with consumption of the product by other consumers.

2. The establishment of a federally funded, independent 800-number consumer hotline. The hotline number should be printed on the label of every NutraSweet product, enabling concerned consumers to easily obtain information about product safety and to easily register their complaints.

3. A moratorium on the approval of new uses for NutraSweet by the FDA. Currently, the manufacturer is requesting that the FDA approve its use in baked goods, while scientific research conducted by Dr. Jeffrey Bada of the University of California (San Diego) raises serious safety concerns about the many by-products produced through heating, the effects of which are unknown on the human body.

4. Adverse reaction monitoring which links reported consumer reactions to new areas of scientific research.

5. The conduct of independent research. The FDA currently determines product approval on the basis of research funded and conducted by the manufacturer of the product. Research should be conducted independently of the company so that results will not be biased. There is much information available which indicates that many adverse health effects were not unforeseen at the time of FDA approval in 1981. (See UPI report, attached).

5. Clinical testing for behavioral/neurological effects. Privately, FDA officials concede that aspartame is a "new generation" of food additive which the agency was not prepared to evaluate properly. In the past, food additives were tested only for toxicity and not for effects on behavior and neurological functioning.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 04 1987

Ms. Lynette M. Bailey
5717 East Broadway
Mt. Pleasant, Michigan 48858

Dear Ms. Bailey:

President Reagan has asked us to reply to your July 8, 1987 letter concerning aspartame.

Since the approval of aspartame for carbonated beverage use in 1983, the media has carried a number of programs and articles which dramatically question the safety of aspartame. These programs often cite the need for more careful study, and raise serious doubts about the thoroughness of our safety review of the sweetener. However, it is not generally realized by the public that the initial 1981 approval of aspartame followed only after more than a decade of careful safety and procedural review of test results by our and other scientific experts. Few other food additives have ever had such close scrutiny. Our conclusion that aspartame is safe is supported by an extraordinarily broad range of studies in both animal and man.

Although the sweetener's safety has repeatedly been challenged by its critics, no scientific evidence has come to light which demonstrates that aspartame might be harmful to consumers from the amounts likely to be consumed in foods. While no amount of test data can assure the absolute safety of any substance, our confidence in the safety of aspartame is enhanced to a significant degree by the very nature of its chemical structure. Unlike previous synthetic sweeteners, aspartame breaks down in the body to components which are the same natural constituents found in many foods we eat.

Within the past few years, possibly as a result of the media programs on aspartame, we have received a number of consumer complaints ascribing a wide variety of adverse health symptoms to aspartame. In 1984, to help us gauge the significance of these reports, we enlisted the aid of the Centers for Disease Control (CDC) to assist us with an indepth review of some 600 case studies documented by the Food and Drug Administration field investigators. From the enclosed summary of the CDC's report, you can see that we did not find evidence that aspartame was associated with a significant public health risk.

However, the CDC report also suggested that there may be a small but significant population of consumers who are "sensitive" to aspartame. This sensitivity to aspartame is presumably similar to the adverse response experienced by some individuals to various other food and color additives, as well as to certain foods. Clinical studies are planned and underway to help clarify the nature of these reported adverse effects. At the present time headache appears to be the most common complaint. We have no documented information which indicates that any of the reported health effects are irreversible once the use of the sweetener is discontinued.

Thus, although we have no indications from preapproval studies that the use of aspartame might cause adverse effects, it does not preclude their occurrence in a small segment of users. We encourage continued documentation that physicians can provide that supports the relationship of symtomatology to aspartame ingestion.

If we can be of any further assistance, please let us know.

Sincerely yours,

Mary L Richardson /for

Hugh C. Cannon
Associate Commissioner
for Legislative Affairs

Enclosure
CDC Summary

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(Editor's note: UPI investigative reporter Gregory Gordon spent eight months examining industry research into the popular artificial@ sweetener NutraSweet and the Food and Drug Administration's handling of the product permeating the diet food and drink markets. Here is the first in his three-part report.)(

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Part 1: Did Searle ignore early warning signs?(
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By GREGORY GORDON@(

WASHINGTON (UPI) _ A University of Illinois scientist says he warned the G.D. Searle Co. years before NutraSweet swept the diet food and soft drink markets that the company's new artificial sweetener could heighten risks of brain damage in fetuses and small children.(

Dr. Reuben Matalon, a pediatrician and geneticist, said that between 1976 and 1984, he prodded Searle officials several times to do more research on the issue but Searle never performed the studies he suggested.(

The Chicago-based company did, however, pursue U.S. government approval for the low-calorie sugar substitute _ and got it in a controversial ruling in 1981.(

Today, tens of millions of Americans guzzle diet soft drinks stamped with the NutraSweet ``Swirl,'' dump packets of the NutraSweet tabletop sweetener ``Equal'' in their coffee and consume NutraSweet-flavored cereal, puddings, gelatins, cheesecake, chewing gum or vitamin tablets.(

The Food and Drug Administration, despite receiving more than 3,
consumer complaints, is so confident of the sweetener's safety that it recently expanded uses to frozen and chilled fruit juices.(

Matalon, however, has remained skeptical. In May, he reported th
his initial, federally funded tests on 51 adults suggest heavy NutraSweet consumption may increase blood levels of a key amino acid enough to affect attention span, memory and concentration in some people, particularly small children. Pregnant women who are sensitive to the sweetener's main component, the amino acid phenylalanine, also may face a heightened risk that their infants will have birth defects, Matalon said.(

More than a dozen other scientists, some of whom are conducting clinical studies, also say they suspect that subtle effects of the sweet powder could pose a major health problem. They believe NutraSweet _ known generically as aspartame _ is linked to brain damage, epileptic seizures, eyesight problems, allergic reactions, headaches or dizziness.(

``The likelihood is very strong that aspartame does produce seri
and potentially damaging brain effects in a number of people,'' said Richard Wurtman, a neuroscientist at the Massachusetts Institute of Technology who is studying scores of people who suffered seizures after using NutraSweet.(

Facing continuing controversy, The NutraSweet Co., the name adop
by Searle's NutraSweet division following its 1985 sale to the giant Monsanto Co., vouches for the sweetener.(

The firm's president, Robert Shapiro, rejects the criticism voice
by Matalon and others, saying, ``The fact is that the world scientific community has considered these very specific allegations repeatedly, and has come to the same conclusion as the FDA.''(

An eight-month United Press International investigation not only turned up scientific concerns, but also raised questions about the way the product was approved, about the independence and depth of industry-funded research efforts into its safety, and about ``revolving door'' relationships between FDA officials _ including former commissioner Arthur Hull Hayes Jr. _ and the food and drink industries.(

Shapiro, who obtained an advance copy of this UPI report, said, ``Taken as a whole, the effect of the article is likely to be a thoroughly misleading impression of the state of knowledge of the subject.''(

Company spokesman Thym Smith said the firm is contemplating litigation.
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Sen. Howard Metzenbaum, D-Ohio, a leading skeptic of the FDA's approval who plans to hold a hearing on NutraSweet in the next few weeks, said, ''I don't have hard evidence that the product is not safe. But I'm convinced that there's no hard evidence ... that the product is safe.'' (

FDA officials stress they have yet to see hard data disproving the sweetener's safety. For that reason, the agency last year rejected a consumer group's petition to ban it on grounds that 140 users suffered seizures and eye problems. (

NutraSweet has been at the center of intense controversy almost since July 18, 1981, the day Hayes approved its use in dry foods. (Indeed, in rendering his decision, Hayes overrode six of the nine scientists on two agency review panels who felt studies on its possible link to brain tumors in rats had been inadequate. ^more(

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Since then, some independent scientists have become unusually outspoken. Drs. Louis Elsas of Emory University and William Pardridge of the UCLA Medical School charged that the diet food and drink industry has engaged in a ''whitewash'' by rejecting health concerns, manipulating research studies and wining and dining scientific critics. (

These and other researchers describe a world of subtle, high-stakes strategy in which the availability of corporate funds and the design of research protocols may have influenced the course of a multibillion-dollar industry and potentially affected the safety of millions of people. (

The NutraSweet Co. and a non-profit industry group reject these allegations, asserting they have commissioned scores of studies to test the product's safety and that decisions on research funding are made solely on merit. Company spokesman Smith said NutraSweet's ''phenomenal safety record is the result of the well known nature of the product rather than the manipulations of management.'' (

Consumer complaints about NutraSweet surged in 1983, after Hayes' deputy, Mark Novitch, with the commissioner's support, approved its use in soft drinks such as ''Diet Coke'' and ''Crystal Light,'' sending consumption soaring. (

UCLA's Pardridge noted in a letter to the American Medical Association Journal last year that, with aspartame, the food industry now is adding about five million pounds of phenylalanine _ ''a known neurotoxin'' t'emistry _ to the food supply every year. (

Roy Burry, an analyst with Kidder-Peabody, Inc., said the exploding diet market now accounts for 24 percent of soft drink sales, compared with 10 percent in the late 1970s, and is growing at 20 to 25 percent a year. (

The NutraSweet Co.'s sales are no longer public, but last year revenues were believed to have exceeded previously stated levels of $700 million. (

So intense has been the NutraSweet advertising campaign that the diet food and beverage industry created a ''NutraSweet World Professional Figure Skating Championship.'' (

''Taking good care of oneself makes life a little better _ and NutraSweet makes it a little sweeter!'' boasted one ad during a TV fitness program. (

The NutraSweet Co. also has paid up to $3 million a year for a 100-person public relations effort by the Chicago offices of Burson Marsteller, a former employee of the New York PR firm said. The employee said Burson Marsteller has hired numerous scientists and physicians, often at $1,000 a day, to defend the sweetener in media interviews and other public forums. Burson Marsteller declines to discuss such matters. (

Dismissing safety fears, The NutraSweet Co. stresses that its product, which in raw form is 180 times sweeter than sugar, has been endorsed by the AMA and other scientific bodies worldwide. Actually, the AMA's Council of Scientific Affairs gave a qualified endorsement based on ''available evidence,'' including company-funded studies that were challenged by FDA task forces during investigations of the firm's laboratory practices in the 1970s. (

Of 69 scientists who responded to a recent General Accounting Office survey, 28 said they felt more research was needed on NutraSweet and a dozen of those questioned considered it a major health problem. (

An ''aspartame victims'' group has formed, a consumer group has pressed legal challenges and the company faces at least three personal injury suits. In one suit, Jim Stoddard, 32, a diabetic in Grand Rapids, Mich., charged that his heavy NutraSweet consumption triggered a dozen seizures _ the last one so violent he dislocated his shoulder and fractured his collar bone. (

Stoddard's lawyer, his sister, Cynthia, alleged he suffered brain damage and now has trouble understanding words because he consumed a product inadequately tested by Searle. She said she withdrew the suit recently for tactical reasons but would refile it early next year. The company denies the allegations. (

Wurtman, who quit his job as a Searle consultant and became a voca NutraSweet opponent, said he has been contacted by more than 200 persons who suspect they suffered seizures as a result of NutraSweet use.(

He said Dr. Gerald Gaull, a Searle vice president, visited his laboratory in 1985 and threatened to veto funding by ILSI, the Washington-based tax-exempt foundation, for his planned study into whether NutraSweet changes brain chemistry, lowering some humans' seizure threshholds.(

Gaull said ``there's no way'' Searle, with one of 12 votes on the ILSI panel, could veto a grant decision, but he did not deny making the threat.(

ILSI ultimately turned away Wurtman on grounds that Searle already had arranged for seizure studies at Yale University and New York's Mount Sinai Hospital _ studies that have drawn criticism because human volunteers were given aspartame only once or twice.(

Wurtman said he now is tapping his laboratory's budget, which is extremmely limited, slowing progress on his own studies. ``Aspartame may be a serious health hazard,'' he said. ``It's critically important that high quality research now be done to assess this hazard.''(

In his letter to the AMA Journal, Pardridge said no one has fully researched the degree to which aspartame raises phenylalanine levels in the brain and, if so, what the possible effects are. He said in an interview that after he raised questions about the sweetener's effects on children, ILSI rejected his two grant proposals in 1985. Last year, he said, Gaull pressed him at a conference in Colorado to prove that phenylalanine _ one of 21 amino acids _ causes brain damage. ^ more(

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''It was incredible for him to ask that,'' Pardridge said. ''That was the basis for my ILSI grant (proposal).''(

''There's an internal conflict of interest,'' he said, ''when a company which has profit at the bottom line is charged with finding out the true safety of its product.''(

Elsas, who publicly assailed NutraSweet in 1985, said he was put off for a year before ILSI rejected his proposal without stating a reason.(

ILSI's executive director, Jack Filer, asserted research proposals were rejected because they cost too much or lacked scientific merit.(

While denying funding for these aspartame skeptics, the company and ILSI have financed researchers with whom they have long-running relationships. A number of industry-funded scientists acknowledged that company and ILSI officials originated ideas for their studies or participated in the research design. These studies generally have reported the sweetener is safe.(

Consumer lawyer Turner said, ''The notion that an industrial company would take large sums of money and parcel it out to scientific consulting firms and university departments ... who they consider to be personal and commercial allies and friends is an unconscionable way to insure the safety of the American food supply.''(

He said the NutraSweet experience shows that ''the entire system of the way scientific research is done needs to be carefully investigated, evaluated and revamped.''(

Food industry officials also said most studies financed by Searle or The NutraSweet Co. have been arranged as contracts, rather than grants. Smith said the company often uses contracts ''to accomplish a specific research task.''(

James Scala, former director of health sciences for the General Foods Corp., a major NutraSweet user, said that a scientist working under contract became ''more of an arm of the Searle research group than a grantee.''(

Scala, now with the Shaklee Corp., also said that most early NutraSweet research consisted of short-term studies that ignored possible ''subtle,'' long-term effects.(

Matalon said, ''Let us say cigarettes were invented today, and you give 20 people two packs a day and after six weeks, no one has cancer, would you say that it is safe? That's what they did with NutraSweet.''(

Dr. Martha Freeman, who was a medical officer at the FDA's bureau of drugs in the early 1970s, argued in 1973 that^ @the substance was ''a new chemical ... that doesn't occur naturally'' and should only be approved after long-term clinical studies, as if it were a new drug. Her arguments were rejected.(

Despite these complaints, The NutraSweet Co. has insisted that company-funded studies prove that except for people with the rare disease phenylketonuria, the human body processes phenylalanine in aspartame just like any other food.(

Thomas Stenzel, a spokesman for the International Food Information Council, a public relations arm for NutraSweet's manufacturers and biggest customers, contended scientific adversaries comprise a small minority.(

He said he found it ''very important that the leading professional health organizations'' have found NutraSweet to be safe.(

For example, the American Academy of Pediatrics concluded in 1985 that studies on people given massive aspartame doses showed no dangerous rise in blood phenyalanine levels; the Epilepsy Institute has reported the sweetener ''to be safe for people with epilepsy.''(

Filer, executive director of the industry's main organ, the International Life Sciences Institute, suggested that problems blamed on aspartame may stem from ''water load'' on the brain resulting from over-consumption of liquids.(

Maj. Michael Collings, who was an Air Force F-16 pilot in top physical condition, said he often drank up to a gallon of aspartame-sweetened products when he finished his daily, five- to eight-mile jogs in Nevada's desert heat. After noticing slight trembling in his hand over several weeks, he collapsed unconscious with a seizure on Oct. 4, 1985, a lawyer for Collings said. (

Because of the seizure, Collings is grounded as a pilot for life, is on medication and was ordered transfered to Maxwell Air Force Base in Alabama at a $400-a-month pay reduction, said attorney Bryan Gould, who charged in a state court suit last year that NutraSweet caused the seizure. (

''He tells me that there's no way to describe the feeling of flight,'' Gould said. ''He loves to fly and now he can't.'' The NutraSweet Co. denies any link between the sweetener and Gould's medical problems. (

FDA officials, while publicly endorsing aspartame, are watching the situation closely. In late 1985, the agency took the unusual step of asking doctors nationwide to report adverse reactions to NutraSweet and another food additive, sulfites _ a move normally reserved for drugs. Sulfites since have been banned from the market. An FDA spokesman said about 25 doctors filed reports suggesting aspartame links to varying health problems. ^ more(

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The FDA approved NutraSweet products on the condition they carry a compulsory warning to phenylketonurics, individuals sensitive to its phenylalanine component. But Matalon, Elsas and others worry about millions of ''carriers'' of the disease who are unaware of their sensitivity. They say NutraSweet could damage fetuses of pregnant women whose bodies have trouble processing the amino acid.(

Matalon, on releasing his new study, urged that products be labeled with the amount of NutraSweet they contain so consumers can monitor their intake. In Canada, aspartame is the only food additive for which such quantity labeling is required.(

With consumption soaring, Sanford Miller, chief of the FDA's bureau of foods, has acknowledged considering a labeling requirement in this country.(

Dr. Gary Flamm, the FDA's top toxicologist overseeing food additives, said that beyond labeling, once a food additive such as NutraSweet has won approval, it is far more difficult to restrict its marketing.(

''If ... our approval of it was a mistake, we couldn't rectify that without data showing that aspartame was unsafe,'' said Flamm, an aspartame defender.(

Even then, he said, the agency would face a new regulatory thicket unless it could be shown NutraSweet posed ''an imminent hazard.''(Consumer lawyer James Turner, who has campaigned for more than a decade for a NutraSweet ban, assailed the FDA's treatment of such safety issues. ''Once a product is on the market, whether there by nefarious or honest means,'' he said, ''it is impossible to get it off the market until it has caused severe, undeniable damage that has probably lasted over many years.'' ^ (

Several independent scientists have alleged that the industry has steered research money to allies in the scientific community, while denying funding to those who have raised health concerns.(

A number of scientists who pressed for more studies into possible brain damage told UPI they were turned away by Searle and the International Life Sciences Institute, a tax-exempt industry foundation supported by the company, its Japanese aspartame-manufacturing partner and 10 sellers of NutraSweet-flavored products.(

In interviews, Drs. Matalon, Wurtman, Elsas, Pardridge and John Olney of Washington University in St. Louis charged that the industry has paid millions of dollars for studies that have skirted the real issues about NutraSweet.(

''There are virtually no studies,'' Turner said, ''that have been done by individuals using resources other than the industry's that have given a clean bill of health to aspartame.''(

University of Illinois researcher Matalon recalled that he couldn't persuade Searle to do the kind of research necessary to put to rest lingering health concerns, neither on his first approach in 1976 nor when he submitted specific grant proposals to four more company officials beginning in late 1980.(

After NutraSweet won FDA approval and began changing the dietary habits of millions of Americans, Matalon said he lost patience in 1984 with the usual encouragement from Searle officials about prospects for future funding. ''I felt they were just stringing me along,'' said Matalon, who obtained a $180,000 grant from the National Institutes of Health.(

Company spokesman Smith said the NutraSweet manufacturer has ''not discouraged Dr. Matalon's work _ nor anyone else's.'' While declining to comment on the decision not to fund Matalon's study, Smith said the company spends ''between $30 (million) and $35 million annually on research.''(

''We do make decisions based on how we understand a study will be conducted and ... reasonable scientists may disagree on study designs,'' he said. The company has alleged that a number of its critics are seeking to pressure the industry to fund their laboratories.(

Faced with sharply differing opinions on the sweetener's safety, the FDA and the National Institutes of Health, the government's chief funding mechanism for private research, have financed few studies on its effects. One former ranking NIH official, Artemis Simopoulos, argued the agency ``should have a very extensive program on aspartame so people would know'' whether it is safe. (

Yet some NIH scientists have served as consultants to the ILSI foundation, helping decide the awards of $500,000 in annual NutraSweet research grants in recent years. Even Simopoulos was a non-paid member of the foundation's board. (

But ILSI's ``aspartame technical committee,'' consisting of the NutraSweet Co. and 11 other manufacturers and users of the sweetener, has been accused of discriminating against NutraSweet critics in granting awards. (

Represented on the ILSI committee are General Foods, the Coca Cola Co., Pepsico, Inc., the Royal Crown Cola Co. and Seven-Up, Inc. ILSI insists that the NutraSweet Co. carries no special weight despite its U.S. monopoly on the sweetener. ``The NutraSweet Co. is one of our members,'' said ILSI administrator Sharon Senzik. ``Committees operate by Robert's Rules of Order.'' (

Filer collaborated for several years on NutraSweet research with a colleague at the University of Iowa, Dr. Lewis Stegink. Filer pledged that, despite his past ties to the company, as ILSI's head he would ``let the chips fall where they may'' on research results. (
Samuel Molinary, co-chairman of ILSI's panel, is Searle's former director of scientific affairs and now Pepsico's research director. Molinary insists that ILSI is not ``a lackey and tool'' of The NutraSweet Co. ^ more(

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Peter Dews, a Harvard University psychobiology professor named to ILSI's original board of trustees in 1978, has served as an ILSI consultant since then. Dews recently took the trouble to write and promote an article declaring that, based on scientific presentations at an ILSI aspartame conference in Spain last year, ``there is now a mass of evidence'' that NutraSweet is safe if consumed at FDA-recommended levels. (

Dews declined to discuss his ILSI consulting fees, except to say it is ``not enough to make any difference in my life.'' ILSI's 1984 return filed with the Internal Revenue Service showed payments to Dews that year of $31,000. (

A lawyer for ILSI pledged to the IRS, in obtaining tax-exempt status for the foundation in 1983, that the organization ``does not have any plans to engage in commercially sponsored scientific research.'' Attorney Roger Middlekauff advised the IRS that ILSI would ``direct the research toward benefiting the public'' and would release all research results. (

But Elsas charged that ILSI ``is definitely a front organization to try to make the public believe that there is some non-directed, non-biased research going on,'' when ILSI studies actually are likely to support NutraSweet's safety. (

The industry has invited scientific critics for paid visits to company laboratories _ sometimes offering courtesy ``honorariums,'' an industry source said. (

The NutraSweet Co. also has hosted critics at conferences in resort settings. Matalon briefed ILSI on his research at a meeting in the Costa del Sol region on Spain's southern coast. In the summer of 1985, the firm flew Wurtman, Elsas, Matalon, Pardridge, several of their wives and other NutraSweet critics to a two-day meeting at a luxurious home in Northeast Harbor, Maine. An afternoon was spent on a yacht, participants said. ``This was industry wooing the concerned to shut up,'' Elsas said. (

Pardridge said he was the only strong aspartame critic to accept an invitation in June 1986 to a heavily attended Searle-sponsored conference at a picturesque ski resort in Keystone, Colo. Pardridge said when he tried during the conference to raise his concerns about phenylalanine, the discussion was cut off. ``It was just another typical industry whitewash,'' he said. (

Next: An approval marred by controversy(

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By GREGORY GORDON=

WASHINGTON (UPI) _ Susan Yarmey, a free-lance writer from Quincy, Mass., woke on a hot July morning in 1984 with a large bump on her head and bruises all over her body.(

''I had no recollection of what had happened. There were marks on the wall, two wooden steps were broken and there was a nice gash in the wall where my head had hit,'' she said.(

Yarmey's doctors diagnosed her injuries as resulting from a ''classic'' epileptic seizure. She and Massachusetts Institute of Technology neuroscientist Richard Wurtman believe the incident may be connected to her consumption of the artificial sweetener NutraSweet, known generically as aspartame.(

''A friend in New York directed me to the possible effects of NutraSweet consumption ... I was probably, at that particular time period, doing a liter and a half to two liters (of diet soda with NutraSweet) a day,'' said Yarmey, who said when she stopped taking NutraSweet her problems disappeared.(

Yarmey is not alone. Many NutraSweet consumers _ particularly heavy users _ who have suffered headaches, tremors, blindness, allergic reactions and seizures blame NutraSweet for their ailments.(

Wurtman says he personally is aware of more than 200 cases in which he suspects NutraSweet has caused health problems such as headaches, dizziness and seizures.(

Wurtman says the problem might be solved simply by stiffening the labeling requirements for NutraSweet products so that certain identified groups can monitor their intake.(

''The groups I would identify are pregnant ladies, small children, people with a history of seizures and people who are taking certain drugs that interact with phenylalanine,'' an amino acid in the sweetener, Wurtman said.(

Another former NutraSweet consumer, Shannon Roth, a mother of two who works as a goldsmith in Ocala, Fla., organized Aspartame Victims and Their Friends, Inc. after suffering blindness in one eye. She said the group now has about 700 members.(

''I got up in the morning and had two packs (of Equal, the NutraSweet tabletop version) in each cup of coffee ... three or four cups of coffee before noon. Then I'd switch to the iced tea with it,'' Roth said.(

In the summer of 1984, Roth said, she began to experience headaches, sleep and memory loss and irritability. After getting out of bed one morning, she discovered that she couldn't see when she closed her right eye, Roth said.(

''I could see like through a black veil. It was like a centralized, almond-shaped black spot,'' she said.(

Doctors' laboratory tests failed to trace the cause of her partial blindness, she said, and one doctor told her not to expect vision to return to her eye.(

Roth said she suspected NutraSweet as the cause after learning of a similar case that was allegedly linked to the sweetener _ and after about four weeks without NutraSweet, her headaches and other problems ceased. Her sight began to return a few weeks later, she said.(

Joyce Wilson, a real estate agent in Stockbridge, Ga., said she began suffering from high blood pressure, dizziness and other ill health effects in 1982 after using Equal in her coffee and eating NutraSweet-flavored puddings. She said that in 1984 and 1985, she lost some vision.(

``I'm not blaming this all on NutraSweet,'' Wilson said. ``I'm just saying it's a strange coincidence that when I started using it, I started falling apart.''(

Dr. Morgan Raiford, an ophthalmologist at Emory University, examined both Roth and Wilson and believes their problems stem from consumption of the methyl alcohol in NutraSweet.(

Dorris Bookhart, 43, a legal secretary in Lodge, S.C., started having what were later diagnosed as temporal lobe seizures in August of 1984. At the time, she said, she was drinking four 16-ounce bottles of Diet Coke a day, as well as diet lemonade. Both contained NutraSweet.(

In January of 1985, after six months of problems, she suffered a grand mal seizure, a convulsive episode in which the victim loses consciousness, she said. Her doctors were mystified by the seizures, but they ruled out epilepsy, Bookhart said.(

She said she suspected NutraSweet as the culprit when, at her husband's suggestion, she stopped drinking Diet Coke and the problems ended.(

``I've cried a lot of times thinking these people have destroyed my life and there isn't a damn thing I can do,'' she said.(

Another heavy user of the artificial sweetener, Larry Taylor of Arlington, Texas, said he was hospitalized for five or six days to undergo a battery of tests after suffering a grand mal seizure in 1985. He also was a victim of migraine headaches that became more frequent between 1982 and 1984. After his seizures, Taylor, an anesthetist, was not allowed to work until January of this year, a disability he said left him ``financially devastated.'' ^ adv mon oct 12 or thereafter(

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What the critics say about NutraSweet(
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By GREGORY GORDON=

WASHINGTON (UPI) _ Despite The NutraSweet Co.'s insistence that scores of company studies have proved the sweetener is harmless, here's a sampling of the concerns from a hard core of scientific critics:(

_Dr. Reuben Matalon of the University of Illinois has reported that heavy consumption of NutraSweet's main component _ the amino acid phenylalanine _ may cause neurological problems such as loss of memory and concentration. Matalon and Dr. Louis Elsas of Emory University say they fear aspartame consumption by some pregnant women can cause irreversible brain damage in fetuses. They worry most about women among an estimated 4 million to 20 million Americans who are carriers of the genetic disease phenylketonuria _ characterized by the liver's inability to process phenylalanine. While there are an estimated 20,000 to 30,000 PKU victims nationwide who are warned not to take NutraSweet, carriers or heterozygotes _ do not have the disease and generally are unaware of their sensitivity, they said. The company has said that the Food and Drug Administration concluded ''NutraSweet did not present any additional health risk to pregnant women.''(

_Dr. Paul Spiers, a clinical neuropsychologist at Boston's Beth Israel Hospital, found in a recent pilot study that, after consuming NutraSweet, some subjects with no previous problems failed to show the usual improvement in performance on cognitive tests. He plans further research. But Dr. Harris Lieberman of the Massachusetts Institute of Technology, who has received industry funding for NutraSweet research in the past, said his study of 20 adult males indicates that aspartame ''has no readily measurable effect on mood and performance in normal humans.''(

_In St. Louis, Washington University allergist Dr. Anthony Kulczycki found that two women given NutraSweet capsules and a placebo suffered allergic reactions to NutraSweet. The women had reported hives and other skin reactions after using the sweetener.(

_Dr. Donald Johns, a neurology resident at Massachusetts General Hospital, reported last year that a ''double-blind'' study of a woman suffering migraine headaches showed her problems were aggravated by consumption of NutraSweet. NutraSweet, known generically as aspartame, consists of phenylalanine and another amino acid, aspartic acid, linked to a small quantity of methyl alcohol. Scientific critics seem to worry most about phenylalanine.(

_Dr. Richard Wurtman, a Massachusetts Institute of Technology neuroscientist, says heavy NutraSweet consumption may so flood the bloodstream with phenylalanine that other essential amino acids are blocked from reaching the brain, causing chemical changes that can affect behavior and lower the threshhold at which many people suffer epileptic seizures. Wurtman and Dr. Donald Schomer of Harvard University are testing seizure victims who used NutraSweet, particularly some whose bodies may have trouble processing phenylalanine. The NutraSweet Co. concedes aspartame raises brain phenylalanine levels, but says no harm results and that consuming the amino acids in NutraSweet ''is just like eating other foods containing the same protein components.''(

_Another Wurtman protege, Dr. Timothy Maher of Massachusetts General Hospital, supported his mentor by reporting that mice given a seizure-inducing drug and NutraSweet suffered more seizures than those receiving the drug alone. Dr. Henry Haigler, a scientist in a NutraSweet Co. sister firm, said his similar study showed ''no effect on seizure threshholds.''(

_Dr. William Pardridge of the UCLA Medical School, who also has done phenylalanine research, said he most fears the sweetener's effect on children, who he says are more likely to approach the FDA's acceptable daily intake level of 50 milligrams per kilogram of body weight. ''If you're a child, seven to 12 years of age, the chances are good you'll have five servings per day'' _ close to the acceptable level, he said. But Dr. Harvey Levy, head of the PKU clinic at Boston's Children's Hospital, wrote the Journal of the American Medical Association that Pardridge made an ''inaccurate interpretation'' of their data in predicting brain damage effects on fetuses from aspartame. Any danger level, they said, ''would seem to be considerably higher'' than levels from NutraSweet consumption.(

_Dr. Woodrow Monte, an Arizona State University food scientist, and Dr. Morgan Raiford, an ophthalmology professor at Emory, worry that a NutraSweet breakdown product, methyl alcohol, could produce severe eye damage. Last year, Raiford examined more than a half dozen persons who said they suffered eye problems after consuming NutraSweet heavily. He said he diagnosed some cases of optic nerve damage and suspects NutraSweet's methyl alcohol is the culprit. The company denies any connection between NutraSweet and eye problems and has offered free exams to consumers who complain of such problems.(

_Dr. Sidney Wolfe, executive director of the Washington-based Health Research Group, said, ``The thing that's really worrisome is that it clearly affects brain metabolism in animals, and anyone who disputes that is irresponsible.''(

_Dr. John Olney of Washington University expresses fears about brain tumors _ a problem he and other scientists say would not show up in humans for 20 years and would be difficult to trace to NutraSweet. Olney said Searle rat studies have shown conflicting brain tumor data. As early as 1971, Olney reported that aspartic acid in aspartame killed cells in the brain's hypothalamus region, which regulates glandular and hormonal functions. ^ adv mon oct 12 or thereafter(

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Company responds to UPI series@(

WASHINGTON (UPI) _ In response to the United Press International series of articles on NutraSweet, The NutraSweet Co. issued the following statement:(

A series of articles to be released this week by UPI seriously misrepresents the vast body of scientific evidence which establishes the safety of aspartame.(

Contrary to the impression created by these articles, the scientific record has been carefully reviewed by independent and official scientific and regulatory agencies around the world.(

Without exception, each of these agencies has concluded that aspartame is a safe sweetener which can be used as a normal part of the daily diet.(

The following quotations are representative of expert scientific and medical opinion around the world.(

U.S. Food and Drug Administration: ``The data and information supporting the safety of aspartame are extensive. It is likely that no food product has ever been so closely examined for safety ... Few compounds have withstood such detailed testing and repeated close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety.''(

American Medical Association Council on Scientific Affairs: ``Consumption of aspartame by normal humans is safe ...''(

American Diabetes Association: ``Aspartame has been determined to be safe for the general population as well as for people with diabetes.''(

Government of Canada (Health Protection Branch): ``(Aspartame) is one of the most extensively studied chemicals permitted for use in food. ... Based on the available data it has been concluded that aspartame would not pose any hazard to health when used in accordance with the current provisions of the Canadian food and drug regulations.''(

Government of Denmark (Danish Food Institute): ``Research publishe in the scientific literature and/or studied in detail by governments and independent scientific committees maintains that the use of aspartame as an additive does not bear any health risk at all. ... There is therefore no toxicological basis for believing the intake of aspartame in soft drinks and food products should give rise to harmful effects in children or adults, even people with a high level of useage.''(

Government of Great Britain (UK Committee on Toxicity of Chemical: and Food): ``Following detailed consideration of all toxicological data, we see no objection to the use of aspartame in food.''(

Other scientific agencies that have reviewed the evidence and confirmed the safety of aspartame include the World Health Organization of the United Nations; the Scientific Committee on Foods of the European Common Market; the Epilepsy Institute; and the American Academy of Pediatrics.(

Aspartame has been reviewed and approved as a safe sweetener by t official food regulatory authorities in all the leading nations of the world, including many which forbid or restrict the useage of other sweeteners.(

A recent article by Harvard Medical School Prof. Peter Dews reviewed the ``massive evidence'' that establishes the safety of aspartame. Dr. Dews concluded: ``Many articles of everyday consumption that are known to be safe might not survive the scrutiny of such intensive and continued investigation.''(

The respected consumer publication Consumer Reports summarized it conclusions this way: ``An objective weighing of the evidence suggests that aspartame is the artificial sweetener to be preferred on safety grounds.''(

The UPI articles also seek to discredit the process by which aspartame was reviewed and approved by the FDA. These charges have been conclusively rebutted by both the FDA itself and by the General Accounting Office, the investigative agency of the Congress. A full GAO report on the approval process concluded that the FDA had properly followed the appropriate procedures and had adequately addressed the scientific issues.(

The UPI series is replete with misstatements and distortions whic convey a totally misleading impression of the scientific facts.(

Any concern or anxiety by consumers who read these articles is absolutely unwarranted. Aspartame is safe as approved by FDA and regulatory authorities around the world. Any contrary impression created by the UPI articles is a serious disservice to the public.(

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(Editor's note: UPI investigative reporter Gregory Gordon spent eight months examining industry research into the popular artificial sweetener NutraSweet and the Food and Drug Administration's handling of the product permeating the diet food and drink markets. Here is the second in his three-part report.)(

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Part 2: NutraSweet approval marred by controversy(
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By GREGORY GORDON=

WASHINGTON (UPI) _ Poring over laboratory rat studies in the spring of 1981 in the government's final safety review of a new artificial sweetener, senior statistician Satya Dubey of the Food and Drug Administration was troubled.(

Dubey, a member of a special FDA ''commissioner's team'' formed to help decide the fate of the product to be known as NutraSweet, wrote in an internal memo that brain tumor data from rat tests was so ''worrisome'' he could not recommend approval.(

Two other statisticians on the six-member team agreed with Dubey that the Chicago-based G.D. Searle Co. had not proved with ''reasonable certainty'' the safety of the sweetener, known generically as aspartame. A 1980 Public Board of Inquiry had voted 3-0 to ban aspartame because of similar fears.(

But a few weeks later, on July 18, 1981, new FDA Commissioner Arthur Hull Hayes Jr., a pharmacologist who had been in office less than three months and had little background in food additives, overturned the board and approved the use of aspartame in dry foods.(

The ruling, one of the first regulatory actions of the Reagan presidency, came at a time of growing concern that the most widely used low-calorie sweetener, saccharin, was linked to cancer. Thus Hayes' approval of NutraSweet profoundly changed the eating habits of millions of Americans, handing Searle a financial bonanza.(

It also climaxed a topsy-turvy, eight-year FDA review process in which the agency approved the sweetener, then banned it and demanded a grand jury investigation of its manufacturer, only to reverse course again after reexamining the issue at least five times.(

Now six years after Hayes' ruling, its uses expanded, the sweetener is widely consumed in diet sodas, puddings, cereal, drink mixes and even chewing gum and vitamins. Yet NutraSweet and its FDA approval remain at the center of controversy, the sweetener's safety questioned by a small corps of independent scientists; defended by its manufacturer and the diet food and drink industry.(

In a recently released report, the General Accounting Office concluded that the FDA ''adequately followed'' its food additive approval process on NutraSweet. Congress's investigative arm did not evaluate the sweetener's safety. A federal appeals court also has rejected court suits by consumer groups challenging the NutraSweet approval.(

United Press International has learned that more than 10 federal officials involved in the NutraSweet review have taken private sector jobs linked to the industry _ among them Hayes, an acting FDA commissioner and former chiefs and acting chiefs of the agency's Bureau of Foods.(

In addition, many of the scientists who have produced favorable studies or served as outspoken advocates of NutraSweet's safety have received grants or consulting fees from Searle and the industry.(

Consumer lawyer James Turner, who has unsuccessfully pressed petitions for a NutraSweet ban as part of an 11-year campaign against the sweetener, asserted, ''NutraSweet is an opportunity for the entire country to look in great detail at how we make food safety decisions. It is a rickety, 19th Century process.''(
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G.D. Searle began to study the artificial sweetener aspartame soon after a company laboratory chemist, James Schlatter, stumbled on the compound when he licked it off his finger while conducting ulcer research in 1965.(

In a memo on Dec. 28, 1970, a Searle official laid out a plan for winning FDA approval for the sweetener. ''We must create an affirmative atmosphere in our dealing with them,'' Herbert Helling wrote senior company executives. (

Helling suggested that Searle representatives carefully order proposals to the FDA to put Bureau of Foods officials ''into a yes-saying habit.'' If FDA officials could be swayed to do Searle some favor, he asserted, it would ''help bring them into a subconscious spirit of participation.'' (

On July 26, 1974, just 15 months after Searle petitioned for approval, FDA commissioner Alexander Schmidt approved aspartame use in dry foods, allowing a 30-day period for public hearings and comment. He acted on a strong endorsement from the Bureau of Foods, now called the Center for Food Safety and Applied Nutrition. (

At that point, consumer attorney Turner, author of a 1970 book about food additives, objected to the short comment period. Turner was joined in his protest by a now-defunct public interest group and by Dr. John Olney, a Washington University neuropathologist who had linked aspartame to brain lesions in mice. (

Schmidt promptly froze the approval. In an action that was the first of its kind, he ordered that a Public Board of Inquiry be named to look into aspartame. (

Schmidt also had been alerted to conflicts between Searle's research reports and conclusions from independent animal studies that the firm's anti-infective drug Flagyl and its cardiovascular drug Aldactone may cause cancer. He named a Bureau of Drugs task force to investigate. (

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Philip Brodsky, the unit's since-retired lead investigator, said aspartame was included in a broad inquiry into Searle animal studies on five drugs and the Copper-7 intrauterine device to surprise the company ''We didn't think they'd expect us to cover it.'' (

The task force assailed Searle's conduct of research on most of the products, including aspartame, in a searing, 84-page report. (

''At the heart of the FDA's regulatory process,'' the report said, ''is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the G.D. Searle Co., we have no basis for such reliance now.'' (

The task force charged, for example, that the company removed tumors from live animals and stored animal tissues in formaldahyde for so long that they deteriorated. Instead of performing autopsies on rhesus monkeys that suffered seizures after being fed aspartame, the company had financed a new monkey seizure study with a different methodology that showed no problems. (

For the next seven years, Searle's petition was tied up in reviews by the task force and other sharply critical FDA panels. (

At the task force's request, Richard Merrill, the FDA's general counsel, demanded in a letter that Samuel Skinner, the U.S. attorney in Chicago, open a grand jury investigation of Searle and three of its employees. (

One Searle official named by Merrill was Robert McConnell, who had been director of Searle's Department of Pathology and Toxicology and oversaw most of the company's aspartame research. (

McConnell's Detroit lawyer, Gerald Wahl, said that as the inquiries heated up, his client suddenly was awarded a $15,000 bonus and asked to take a three-year sabbatical by director Wesley Dixon. Wahl said Dixon told McConnell he had become a ''political liability,'' a remark Dixon later denied making. (

McConnell received his annual salary of more than $60,000 during the sabbatical at the Massachusetts Institute of Technology, but he never got his job back and ended up suing the company, Wahl said. (

''I've represented hundreds of executives, but I've never seen anybody get the deal that McConnell got,'' he said. ''When you boil it all down, they were looking for continued support from McConnell'' during the inquiries.'(

Wahl said McConnell had felt pressure to hurry his research because of the ''profit motive,'' but that the company never ordered him to alter test results. (

Chief investigator Brodsky said that ''politicized'' handling of the task force disclosures, at hearings chaired by Sen. Edward Kennedy, D-Mass., was one reason he retired in 1977. He said the main witnesses, Searle executives and top FDA officials uninvolved in the investigation, gave ''the wrong answers to the wrong questions ... They didn't even let the experts answer the questions.'' (

The FDA, rocked by the controversy, established a set of ''good laboratory practices'' _ minimum standards for future corporate research work. (

Richard Ronk, deputy Bureau of Foods chief, stressed that Searle' practices were typical of the industry at the time, not ``the worst on the block.''(

Searle's fortunes did not begin to change until 1977, when Donald Rumsfeld, White House chief of staff under Gerald Ford, was named its new president.(

Turner alleged that Searle chose, with Rumsfeld's hiring, not to redo the questioned studies on the belief he could handle aspartame as ``a legal problem rather than a scientific problem.''(

The company also hired another Ford White House official, William Timmons, as a Washington lobbyist.(

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Before deciding on Merrill's grand jury request, U.S. Attorney Skinner and an aide agreed in February 1977 to meet with lawyers for Searle, including Newton Minow, a partner in the law firm of Sidley & Austin.(

A month later, Skinner, a Republican appointee who was looking fo a job as a result of Jimmy Carter's election, informed aides in a memo that he had begun preliminary employment discussions with the law firm.(

Withdrawing from the Searle matter, Skinner suggested his designated successor, Thomas Sullivan, be left to decide whether to open a grand jury inquiry _ a move that delayed action for at least four months. Sullivan took office just 12 weeks before expiration of the statute of limitations for prosecuting alleged false statements on aspartame. While a grand jury inquiry ultimately was convened, those allegations were not explored.(

Skinner has denied any conflict of interest.(

Assistant U.S. Attorney William Conlon worked with the grand jury until Oct. 12, 1977, two days after the statute of limitations expired on the aspartame allegations. No indictments were brought on the few matters investigated. Conlon, who declined comment, joined Sidley & Austin 15 months later.(

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Following issuance of the task force report in March 1976 and facing a dilemma as to how to proceed, the FDA sought new reviews of several ``pivotal'' studies _ long-term animal tests to see whether aspartame causes cancer.(

A new, five-member internal FDA task force analyzed three of these studies, and Universities Associated for Research and Education in Pathology, Inc., a consortium formed by 15 universities, was contracted to look at another dozen. Much like the earlier team, the five-member FDA task force, headed by veteran Chicago inspector Jerome Bressler, assailed the quality of animal tests into whether the substance might cause birth defects and tumors. ^ more(

The report said Searle laboratory employee Raymond Schroeder, who worked on related research, first told investigators the feed in a study of the aspartame breakdown product DKP was so inadequately mixed it appeared the rats could ``discriminate'' and avoid eating the DKP.(

Schroeder, who has worked for another company since 1975, later backed off his statement. He told UPI, ``I just didn't feel qualified to speak on something I didn't work on ... There's no one twisting my arm.''(

Bressler criticized the company's ``sloppiness'' on all three studies.(

``The question you've got to ask yourself,'' he said in an interview, ``is: Because of the importance of this study, why wasn't greater care taken? The study is highly questionable because of our findings. Why didn't Searle, with their scientists, not closely evaluate this, knowing fully well that the whole society, from the youngest to the elderly, from the sick to the unsick ... will have access to this product?''(

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Howard Roberts, acting director of FDA's Bureau of Foods, appointed a five-person task force to review the Bressler team's findings pending a decision on whether to throw out the three tumor and birth-defect studies.(

Jacqueline Verrett, the senior scientist on the review team, said members were barred from stating opinions about the research quality.(

``It was pretty obvious that somewhere along that line they (bureau officials) were working up to a whitewash,'' she said. ``I seriously thought of just walking off of that task force.''(

Verrett, now a private consultant, said that she and other members wanted to ``just come out and say that this whole experiment was a disaster and should be disregarded.''(

But on Sept. 28, 1977, the panel reported that deviations between Searle's raw data and its FDA submissions were ``not of such magnitude'' as to alter its conclusions.(

Verrett said the bureau's intent seemed to be to tone down what was really found.'' She noted the bureau felt pressure because safety concerns also had been raised about cyclamate, another alternative for the cancer-linked sugar substitute saccharin.(

(In October, 1978, a year after ordering the review that helped get Searle's petition back on track, Roberts quit to become a vice president at the National Soft Drink Association. The NSDA's members later marketed a stream of NutraSweet-flavored diet soft drink products.(

(Reached at NSDA, Roberts dismissed Verrett's criticism, asserting the task force report ``really'was of no importance.'' He said he had no concerns about the appearance of his taking an industry job, stressing he does not represent NSDA before the FDA.(

(``I sleep well at night,'' he said.)(

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Negotiations for an additional, outside review of Searle's studies had begun with an Aug. 4, 1976 meeting between Searle and 10 FDA officials. During the meeting, Searle officials said they desired to help pick the consultant to perform the review, an internal FDA memo said.(

Agency memos show the FDA soon was negotiating with the Universities Associated for Research and Education in Pathology for a half-million dollar, company-funded ``validation'' of a dozen Searle studies.(

The pathology organization's review concluded that Searle's studies were authentic and the discrepancies largely inconsequential.(

Adrian Gross, an investigative consultant to the 1975 task force, later said the 16-month review was ``at best irrelevant'' because the group was limited to analyzing ``whether Searle lied about the data in its tests.''(

``It was not our task to challenge the validity of the experimental methods, since the FDA had itself already accepted the methodology,'' the group's executive director, Kenneth Endicott, said.(

Jere Goyan, who was FDA commissioner in 1980, said he would have put less weight on the review than on the findings of FDA's task forces. Goyan also suggested that, after approving aspartame in 1974, the FDA's Bureau of Foods may have ``felt they had to keep their previous position.''(

Regardless, the pathology group's findings carried major weight in the final approval decision. The chairman of the 1980 Public Board of Inquiry, Dr. Walle Nauta of the Massachusetts Institute of Technology, said the board had to rely on those findings because it was denied access to the task force reports by FDA officials.(

``There was absolutely no way in which we could decide who was right here,'' Nauta said. ``We simply had to accept the data as they stood.''(

Nauta was joined on the panel by Drs. Vernon Young of MIT and Peter Lampert of the University of California at San Diego.(

Before voting 3-0 to ban NutraSweet on the narrow cancer issue, the board itself was drawn into allegations of bias because two of the three members came from MIT _ as did Bureau of Foods chief Miller and several scientists involved in the controversy.(

Between 1979 and 1982, four more FDA officials who participated in the approval process took jobs linked to the NutraSweet industry: Pape; acting FDA commissioner Sherwin Gardner; Albert Kolbye, who was associate director of the Bureau of Foods for toxicology, and Mike Taylor, an FDA lawyer who represented the bureau before the Board of Inquiry. All four denied any conflict of interest.(

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After the Board of Inquiry ruled against NutraSweet on Sept. 30, 1980, Searle waited until Jan. 21, 1981, the day after President Reagan's inauguration, to press for a reversal of the FDA commissioner _ assuring the new administration would decide the issue.(

Jere Goyan, Hayes' predecessor as commissioner, said he found the delay curious because, after eight years of legal battles, financially struggling Searle ``obviously was most anxious to have this thing approved.''(

Robert Dormer, a lawyer for The NutraSweet Co., said there was nothing special about the Jan. 21 date or the papers filed that day.(

But with Reagan's election, it was virtually assured that a Republican-appointed commissioner would replace Goyan and decide the appeal _ and Searle had strong GOP connections with Rumsfeld at the helm.(

Goyan had set up a five-member ``commissioner's team'' of scientists with no prior involvement in the issue to review the board's ruling.(

On May 18 and 19, 1981, a month after Hayes took office, scientists Satya Dubey, Douglas Park and Robert Condon each laid out concerns about the sweetener's safety in memos to team lawyer Joseph Levitt. (

Dubey not only expressed reservations about the reported incidence of brain tumors in one key Searle rat study, but also said key data in another study appeared to have been altered. Dubey, who still works at FDA, refuses to discuss the matter. (

Condon, another statistician on the team, and Park, staff science adviser in the agency's Office of Health Affairs, each said the available evidence failed to prove NutraSweet's safety or lack of safety. (

Park said that Levitt hurried the panel to decide the issue. ''They wanted to have the results yesterday,'' he said. ''We really didn't have the time to do the in-depth review we wanted to do.'' (

Park said Levitt met frequently with Hayes and ''was obviously getting the pressure to get a resolution and a decision made.'' (

Sources have said the office of Sen. Howard Metzenbaum, D-Ohio, has received allegations of political influence in Hayes' final decision-making process. (

In a letter written after the FDA cleared NutraSweet, one former Searle saleswoman, Patty Wood-Allott, asserted that Rumsfeld told his sales force shortly after Reagan took office that, if necessary, ''he would call in all his markers and that no matter what he would see to it that aspartame would be approved that year.'' Rumsfeld declined to return phone calls. (

With three of five scientists on the commissioner's team opposing approval, it was decided to bring in a toxicologist for his opinion on isolated issues. (

Goyan said if the decision were his, he never would have enlarged the team. While the panel did not vote, it ended up split 3-3. (

Levitt, who normally would have been expected to draft an options paper spelling out scientific evidence on key issues, took an unusual tack. He circulated an approval recommendation _ and only backed off when Dubey, Park and Condon objected, team members said. (

Levitt said he was not directed to draft the approval memo, but did so as a ''tactical'' step to break the team's weeks-long impasse by forcing each scientist to state his views. (

''It worked, didn't it?'' said Levitt, who later was promoted to a post as an executive assistant to the FDA commissioner. (

One team member said that during discussions, Hayes, appeared to be abandoning the agency's traditional standard of ''reasonable'' proof of safety and looking for ''proof of hazard.'' (

Hayes' July 1981 approval decision came in the face of a Searle threat to file a suit challenging the regulatory delays. (

His ruling relied in part on a late rat study of brain tumors submitted by Ajinomoto, a Japanese company that manufactures aspartame for Searle. That study, however, tested Wistar rats, a strain that some scientists said is more tumor resistant than the Sprague-Dawley rats used in earlier research. (

In his decision, Hayes wrote: ''Few compounds have withstood such detailed testing and the repeated close scrutiny and the process through which aspartame has gone should provide the public with confidence of its safety.'' (

In late 1982, Searle petitioned for FDA approval to use the sweetener in diet soft drinks and children's vitamins. On a day when Hayes was away, Novitch approved the petition, increasing the acceptable daily intake level for humans by nearly half, from 34 to 50 milligrams per kilogram of body weight. (

Novitch, now in private industry, said he and Hayes had worked together on the matter, but declined to say why he was left to sign the approval. (

Just weeks later, Hayes resigned under the cloud of an internal Department of Health and Human Services investigation into his acceptance of gratuities from FDA-regulated companies _ including free rides aboard jets owned by a major NutraSweet user, the General Foods Corp. (

Shortly after being named dean of the New York Medical School, Hayes also became a consultant to the New York-based public relations firm of Burson Marsteller, which represents the NutraSweet Co. and several major users. (

Hayes' former top spokesman, Wayne Pines, who previously had joined the firm, said he approached Hayes because he thought him ''an added value'' to clients. ^ more(

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Hayes, now president of the E.M. Pharmaceutical Co. in Hawthorne, N.Y., declined comment for this series of articles. He has in the past denied any impropriety in his consulting role, which sources said paid him more than $1,000 per day. (

Burson Marsteller vice president Buck Buchwald stressed that Hayes was not involved in NutraSweet issues and worked but 10 to 15 days a year. But a former Burson Marsteller employee, who requested anonymity, said that Hayes was hired precisely because of his decision on NutraSweet and other issues affecting company clients. (

Metzenbaum said it was ''at the very least ... unbecoming, at the very most it probably was inappropriate'' for Hayes to accept the position. (

In July 1986, Anthony Brunetti, a consumer product officer who drafted the 1983 notice approving NutraSweet use in soft drinks, also took an industry job, joining the soft drink association as a science adviser. Brunetti said he cleared the move with the FDA's ethics officer. (

''My situation,'' he said, ''is no different than many, many people ... that go through the revolving door. It can be made to look like there is some duplicity going on. In terms of my own conscience, I have no problem.'' (

Ron Lorentzen, an FDA toxicologist who was asked by current Bureau of Foods chief Sanford Miller to perform a separate, internal review of the agency's handling of aspartame, described it as a ''tortured'' story. (

But despite the myriad questions and revolving door issues, he asserted the FDA responded to each issue ''in a way perfectly reasonable.'' (
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Other questions have arisen over the company and industry's funding of researchers who have invariably supported NutraSweet's safety _ with the exception of people with the rare disease phenylketonuria. Independent studies have often raised health concerns. (

Dr. Lewis Stegink, a pediatrics professor at the University of Iowa who repeatedly has produced studies that he says support aspartame's safety, has received more than $1.3 million in research grants and gifts _ including lab equipment _ from the company since the early 1970s, limited university records show. (

Metzenbaum said, ''If it is a fact that no questions were raised and more than a million dollars was spent, you have to wonder whether their job was done as thoroughly as it should be done.'' (

Stegink's longtime research collaborator, Dr. Jack Filer, serves as executive director of ILSI, the Washington foundation that funds aspartame research. (

Filer said he sees no conflict in his dual roles as ILSI's executive director and a company researcher, but declined to disclose his ILSI consulting fees. He said all the Iowa research money has gone to Stegink. (

Filer also said the company paid him and Stegink ''$2,000 to $3,000'' to edit a book, ''Aspartame,'' about research on the sweetener and another $1,000 or $1,500 to each of 23 contributors, including researchers whose studies helped the company win FDA approval. The book states that ''the extensive research program carried out to demonstrate aspartame safety may serve as a new standard for the study of food additives.'' Filer said he had been ''maligned over the years for taking money from corporations,'' but that the funding source never has influenced his findings. (

Dr. David Hunninghake of the University of Minnesota was picked to study aspartame's effect on the liver by former Searle research director Daniel Azarnoff, once Hunninghake's mentor at the University of Kansas, a Hunninghake associate said. He said Searle helped design the study. (

Susan Schiffman, named to head a Searle-funded Duke University Medical School study into NutraSweet's link to headaches, is a former General Foods and Searle consultant. Her research at Duke, where the medical school has a new Searle Center, has fallen under the office of university vice president William Anlyan, a former Searle director. Schiffman said Anylan had no role in Searle's promise to cover all costs of the study, expected to cost ''hundreds of thousands of dollars.'' She said she took no salary for her work. (

Another industry-backed researcher has been Ann Reynolds, now chancellor of California State University at Long Beach.^ @Olney asserted that in a 1971 study, Reynolds confirmed his findings that the sweetener destroyed nerve cells in infant mice, but Searle did not notify the FDA until 1975 or 1976 _ after the agency's initial review. Dr. Daniel Azarnoff, Searle's former science director, and other Searle officials have denied withholding any studies from the government. (

Reynolds also co-authored a Searle monkey study that contradicted earlier aspartame research leading to seizures in monkeys. Olney alleged that Reynolds, who did not return phone calls, and several other company-funded researchers ''have a pattern of avoiding'' scientific peer review. Industry spokesman contend that few studies by scientific critics of NutraSweet have undergone peer review. But few such clinical studies have been completed because of a funding shortage.(

George Liepa, a nutrition professor at Texas Women's University, said he was required to discuss his findings with Searle before reporting that NutraSweet is safe for diabetics on hemodialysis.(

Dr. David Horwitz, an associate professor of medicine at the University of Illinois who studied NutraSweet and diabetics, said the company did not influence the outcome but, ''The results were favorable ... Obviously, that is perhaps why Searle was eager to fund an additional study of ours.'' ^ Next: Sweet corporate victories(

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Maverick scientist at center of NutraSweet controversy(
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By GREGORY GORDON=

WASHINGTON (UPI) _ Dr. Richard Wurtman was an ardent defender of NutraSweet's safety at public hearings six years ago. Now he is one of the artificial sweetener's harshest critics.(

''I think the likelihood is very strong that NutraSweet does produce serious and potentially damaging brain effects in a number of people,'' the nationally known neuroscientist from the Massachusetts Institute of Technology said in a recent series of interviews.(

Wurtman's seemingly enigmatic flip-flop from a position as a G.D. Searle Co. consultant to a role as a foe urging restrictions on marketing of the firm's best-selling product appears to be much at the center of the controversy over NutraSweet's safety.(

Wurtman says his views simply changed with the evolution of his scientific studies and his growing skepticism of industry's attitude toward research.(

His sometimes stormy relationships with the company and an industry-funded foundation, the International Life Sciences Institute, provide a glimpse of the maneuverings surrounding research into a major food additive.(

Wurtman, a brash-talking, hard-driving head of a major research laboratory, said he unilaterally severed his consulting relationship with Searle in 1985 after he grew concerned about NutraSweet's effects and the company's inaction. He said he rejected several approaches by the firm _ called The NutraSweet Co. since its sale that year to the Monsanto Corp. _ to rekindle the arrangement.(

Wurtman accuses NutraSweet Co. officials of ''misrepresenting'' the nature of company-financed studies into links between the sweetener, generically known as aspartame, and epileptic seizures, of sidestepping key safety issues and of threatening to veto his grant application to ILSI's aspartame committee.(

A spokesman for the company described Wurtman's public attacks as a ''political issue,'' but declined to elaborate.(

Wurtman's relationship with Searle, The NutraSweet Co. and many of the companies that sell NutraSweet-flavored products dates to 1978. Beginning that year, according to public records, ILSI provided more than $200,000 to finance his research on caffeine, a common beverage ingredient that was under FDA scrutiny.(

Wurtman said he found no ill health effects during his caffeine research, and his relationship was ''excellent'' with ILSI _ a spinoff of the National Soft Drink Association.(

During the same period in 1978, he said, he rejected a Searle offer of financial support for research on amino acids. Phenylalanine and aspartic acid, two such amino acids, are the main components of NutraSweet.(

He said Dr. Sanford Miller, chief of the FDA's bureau of foods, later sought his testimony before a 1980 Public Board of Inquiry because he had openly stated his belief that neither glutamate nor aspartic acid, a similar compound to that in NutraSweet, would not cause brain damage. Wurtman strongly defended aspartame at the hearing.(

He said he did not focus on phenylalanine until about 1983 when he learned the FDA was considering expanding use of the low-calorie sweetener _ approved two years earlier for dry foods _ to include carbonated soft drinks.(

From his caffeine research, Wurtman said, he was aware of the exploding soft drink market and concluded ''that the use of aspartame was going to go up considerably.''(

''I was genuinely concerned that there might be an increase in brain phenylalanine levels.''(

Wurtman said that, while phenylalanine is vital to the brain, it can serve as a barrier to 20 other amino acids that provide protein.(

At a meeting in July, 1983, Wurtman said he told National Soft Drink Association officials that ''if you put large amounts of aspartame in soft drinks and people drink as much as I think they will, there are going to be problems.''(

Wurtman said that after the industry accepted his idea for combining NutraSweet with saccharin to cut the danger level, he accepted a Searle offer to serve as a consultant and relations were ''all very friendly and chummy.''(

He said he became convinced that ''these people really want to know the extent to which their product may be a real problem.''(

Shortly after he took the consulting job, he began getting letters from seizure victims who believed their problems stemmed from NutraSweet.(

Wurtman said when he advised Dr. Gerald Gaull, Searle vice president for nutrition and medical affairs, in the spring of 1985 that he thought there was a link, ''there was a very rapid souring of the relationship.''(

During a visit to his MIT laboratory, Wurtman said, Gaull asked to review a proposal for a seizure study by him and his collaborator, Harvard University neurologist Donald Schomer. He charged that when he advised Gaull the pair would seek funding from ILSI, Gaull ''got very angry and said, 'We, meaning Searle, are active members of ILSI and we will veto your study.'''(

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''I was incredulous that he would say it to me, and I was dumbfounded that he would say it in front of witnesses,'' Wurtman said.(

Schomer said he did not recall the comment. Gaull said, ''There is no way that I can veto anything at ILSI,'' because Searle has only one of 12 votes on the ILSI aspartame committee. He did not deny making the threat.(

Wurtman charged that Gaull later advised ILSI that two company-funded seizure studies already were under way, and the foundation declined to approve the grant.(

In July of 1985, Wurtman said, he and three other scientists who had expressed concerns about NutraSweet were among a group invited to Gaull's home in Northeast Harbor, Maine, for a two-day conference.(

''I left there with the conclusion there was no way these people were going to do an honest job in assessing the possibility that aspartame contributed to seizures,'' Wurtman said.(

He said he also was skeptical because, as a company consultant, Searle had asked him to chair its scientific advisory committee _ a role in which the company could use his name to defend the integrity of its own research. But, he said, Searle refused to let him see protocols and data from its studies.(

''They wanted the name, but not the reality,'' he said.(

Frustrated by these developments, Wurtman said he wrote a letter to Robert Shapiro, president of Searle and later of The NutraSweet Co.(

''Dear Bob,'' the letter said, ''I know you'll agree that my value to Searle ... derives in part from my telling the company some things that it would rather not hear ... and then from helping the company to deal with those things.(

''One such thing is that some consumers may develop significant medical symptoms after consuming very large amounts of aspartame, particularly if they happen concurrently to be on low-calorie, low-protein weight-reducing diets.... If Searle-supported studies are going to contribute to our understanding of these people and their symptoms, then the studies have to include them _ and not be restricted to people who have a can or two of soda per day.''(

He said Shapiro never answered the letter. Wurtman said he resigned his consulting role a short time later and rejected company efforts in the ensuing months to reinstate the arrangement. ^ adv tues oct 13 or thereafter(

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(Editor's note: UPI investigative reporter Gregory Gordon spent eight months examining industry research into the popular artificial sweetener NutraSweet and the Food and Drug Administration's handling of the product permeating the diet food and drink markets. Here is the last in his three-part report.)(

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Part 3: Sweet corporate victories(

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By GREGORY GORDON@(

WASHINGTON (UPI) _ In October 1982, Sen. Howell Heflin, D-Ala., proposed an obscure amendment altering the laws covering U.S. patent extensions _ a move affecting only one company and one product, the artificial sweetener aspartame.(

Without mentioning aspartame, which is sold under the name NutraSweet, the Senate passed the amendment to the Orphan Drug Act _ extending the G.D. Searle Co.'s domestic monopoly on aspartame sales for another five years, 10 months and 17 days.(

''We think it is an excellent amendment,'' remarked Sen. Orrin Hatch, R-Utah, wrapping up a five-minute discussion on the Senate floor.(

When the House approved the same language a month later, it all but cinched another $3.5 billion to $4 billion in revenues for the Chicago-based company.(

It helped Searle's stockholders sell the company's assets, including its lucrative NutraSweet division and the two domestic use patents, for $2.7 billion to the Monsanto Co. in the summer of 1985.(

Sponsors of the measure found their campaign committees enriched.(

Heflin's 1984 reelection committee received contributions totaling at least $9,000 from Searle's top officers and its political action committee, more than any others among a long list of Searle beneficiaries in Congress, Federal Election Commission records show.(

Hatch's committee received at least $3,000, the records show.(

Heflin defended his sponsorship of the measure, saying Searle had been victimized by regulatory delays that ate up most of its 17-year patent.(

But a spokesman for the U.S. Patent Office said Heflin's legislation marked one of only a handful of instances in the last three decades in which a company's patent has been extended by a private bill in Congress.(

It also provided a glimpse of the adeptness with which Searle, Monsanto and their lobbyists have guided the artificial sweetener through the obstacles of government regulatory bureaucracies to capture big financial rewards.(

Headed by Donald Rumsfeld, a former Ford White House chief of staff, Searle repeatedly demonstrated its political acumen on other fronts, too, in the years prior to the sale to Monsanto.(

In 1981, the company overcame a controversy-snarled, eight-year review process to win Food and Drug Administration approval for NutraSweet.(

In 1984, Searle parried an assault on the sweetener's safety from Arizona food scientist Woodrow Monte after hiring Gov. Bruce Babbitt's former chief of staff as a lobbyist. Searle officers passed along campaign contributions of $2,000 to a key lawmaker, and the company soon had won passage of legislation crushing Monte's efforts to force tough state restrictions on the sweetener.(

''I don't know of any company that has apparently covered all of its bases as well as has Searle,'' said Sen. Howard Metzenbaum, D-Ohio. ''Whether it has to do with the scientists or lawyers, or non-profit institutions, or universities, or whatever; in every instance, I have found that they have expended their dollars very carefully and very wisely, but without apparent restraint as to the amount.''(

Indeed, besides Searle's hiring of up to a dozen lobbyists, UPI traced nearly $200,000 in federal campaign contributions between 1979 and 1986 from its officers and political action committee.(

The political intervention in the patent process drew the ire of several small companies seeking to enter the aspartame market, triggering charges that a corporate giant benefited from unjustified or preferential treatment.(

''I think it's obvious they (Searle officials) used political muscle,'' Alan Kligerman, president of Lactaid, Inc., a New Jersey diet food manufacturer, said of the patent extension. He said his firm had been interested in manufacturing aspartame until the patent was extended, but ''Searle was well wired in.''(

''It is possible that they (the Senate) did not know what they were passing,'' he said. ''I don't know how they got that through, except with the right phone calls.''(

''I would not hesitate to say,'' Metzenbaum said, ''that the manner in which that five-year extension of the patent rights was put through on the floor of the U.S. Senate was totally inappropropriate.(

''It should not have been done without the entire body being advised that that issue was going to be on the floor of the Senate.''(

Metzenbaum said that the Senate has an ''alert'' system under which all legislation is cleared with individual senators before it is brought to the floor, but the system was bypassed.(

Jerry Ray, a spokesman for Heflin, asserted the offices of key senators _ including an aide to Metzenbaum _ approved the measure before it went to the floor. But Ray offered no explanation for the failure to fully disclose the contents and impact of the measure.(

Ray quoted Heflin, chairman of the Senate ethics committee, as saying Searle representatives never mentioned campaign contributions in asking him to sponsor the amendment. ^ more(

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Heflin said he has ''supported all patent restoration bills'' because regulatory delays have created ''a chronic problem'' in which companies get so little use out of their 17-year patents they are reluctant to put money into research.(

Heflin said in Searle's case, ''almost 35 percent of the patent term had been used on a long series of administrative hearings, trials and appeals (in) which, in the end, the corporation finally prevailed. To not restore some of the patent term lost would unfairly penalize them.''(

G.D. Searle sought an extension of its patent on grounds that the Food and Drug Administration's handling of its aspartame approval petition was ''an unparalleled instance of unnecessary regulatory delay which worked a great injustice to Searle.''(

Critics argue that, to the contrary, the FDA suspended its 1974 approval allowing Searle to market the sweetener because of evidence the company's animal studies were flawed and the results were misrepresented to the FDA in the early 1970s.(

The evidence prompted FDA chief counsel Richard Merrill to ask the U.S. attorney's office in Chicago to open a grand jury investigation into possible fraud by the company.(

While a grand jury investigated similar allegations related to Searle drug products, no such inquiry ever was begun into the aspartame testing.(

But the agency was concerned enough about Searle's research to appoint two task forces, a university research group and a Public Board of Inquiry to review various studies.(

In 1981, shortly after taking office, FDA Commissioner Arthur Hull Hayes Jr. overturned the three-man Board of Inquiry and approved sale of NutraSweet in dry foods. Two years later, Hayes' deputy, Mark Novitch, approved the use of aspartame in soft drinks.(

Kligerman dismissed as ''crap'' Searle's contention it had been victimized by the FDA bureaucracy, which delayed a decision from 1975 to 1981.(

''The FDA had reason for doing this,'' Kligerman said of the intense review process. ''It was not an unnecessary delay. It was Searle's fault that this happened.''(

For Purification Engineering, Inc., of Columbia, Md., which raised money from private investors and built a plant solely to manufacture aspartame for Searle, the congressional action ultimately turned out to be devastating.(

Gary Calton, senior vice president for Purification Engineering, said that on Jan. 4, 1985, Searle notified the firm its contract would not be renewed. Seven months later, the firm was sold to Rhone-Poulenc Co., a French firm.(

My company would have been worth a great deal more if it had not been for that (patent) extension,'' Calton said.(

Calling the action unfair, he said, ``I don't think Congress should go around passing laws making G.D. Searle rich any more than they should go around making me rich.''(

Searle officials declined to discuss the patent extension, but a company lobbyist, former Ford White House official William Timmons, said the company ``felt there was an injustice'' in the delays following aspartame's 1974 approval. He said the company ``took an advocacy role by talking to a lot of members'' of Congress.(

In May of 1984, FEC records show, Heflin's reelection committee received maximum $1,000 donations from Daniel Searle, the chief executive officer of the giant pharmaceutical company; his wife, Dain; William Searle, Searle's brother who was a company director; William Searle's wife, Sally; Suzanne Searle Dixon, a sister of the Searles, and her husband Wesley Dixon, who also was a company director.(

Heflin also received $1,000 from William Searle prior to the general election, and $2,000 in Searle PAC contributions, the FEC records show.(

On Nov. 9, 1982, a week after his reelection and a month after praising the amendment in the Senate chambers, Hatch's committee received $2,000 in contributions from top Searle officers, the records show.(

Sen. Robert Byrd, D-W.Va., who brought the amendment up for a vote on Heflin's behalf, also received a $1,000 campaign contribution from Daniel Searle on Sept. 25, 1981.(

Hatch received contributions of $1,000 each from Daniel Searle, Wesley Dixon and William Searle on Nov. 11, 1982, days after he was reelected to a second term in which he continued as chairman of the Labor and Human Resources Committee that oversees the FDA.(

As chairman of the panel until last January, Hatch repeatedly blocked Metzenbaum's calls for new hearings into the safety of NutraSweet.(

Prior to his reelection, Hatch also received $2,500 in contributions from the soft drink PAC.(

Rep. Henry Waxman, D-Calif., who sponsored the Orphan Drug Act covering research for treating rare diseases and who carried Heflin's patent amendment to the bill in the House, received $1,500 in campaign contributions from the soft drink PAC, including $500 two days before the measure's introduction in the House.(

Like Heflin, Waxman made no mention of aspartame in describing the Senate amendments to the drug act on the House floor.(

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Searle also flashed its political prowess after Arizona food scientist Monte stirred up a furor in 1984 by publicly assailing NutraSweet's safety. ^ more(

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The ensuing events, Monte charged, ``reflected exactly what Searle has been doing all along. They've been buying their way into the hearts and minds of America. They've been using their financial acumen to get their way.''(

Within months, legislative rules were swept aside one day in early 1985 and, in a swift, subtle maneuver without notice to the public, Monte's campaign for state regulations on the sweetener was sidetracked.(

Monte was a leading national advocate in the drive to block marketing of NutraSweet until his own credibility was damaged in 1984 with disclosures he had invested in ``put options'' that would have earned profits if Searle's stock dropped. He now concedes his options trading was a mistake, but denies it influenced his research.(

Monte said he was convinced in 1983, when the FDA okayed use of NutraSweet in carbonated beverages, that the sweetener would break down into poisonous quantities of methyl alcohol in diet sodas left in the Southwest sun.(

Monte, director of the Food Science and Nutrition Laboratories at Arizona State, and two consumer groups petitioned the Arizona Department of Health Services to ban the sweetener.(

Monte said his rat studies had shown that chronic ingestion of methyl alcohol causes brain damage similar to that in humans suffering from multiple sclerosis _ including seizures, amnesia, optic neuritis, numbness and dizziness. In the desert heat, Monte said, methanol degrades faster into toxic methyl alcohol.(

Searle and FDA officials have argued that aspartame contains too little methanol to pose a health hazard.(

Monte said his petition signaled a threat to the company [illegible] could have opened the door for regulatory actions in other states. (

When he and the consumer groups pressed their legal challenge for more than a year, Searle flexed its muscle: (

_The company dispatched a coterie of lobbyists to the state capitol, among them Andrew Hurwitz, Gov. Babbitt's former chief of staff; prominent Arizona lobbyist Charles Pine; company lawyer Roger Thies, and another company official, David West. (

_Between August 23, 1984, and Sept. 21, 1984, company officers Daniel Searle and his brother-in-law, Wesley Dixon, each contributed $1,000 to the campaign of state House Majority Leader Burton Barr, later a GOP candidate for governor, reports to the Arizona secretary of state's office show. (

Campaign disclosure forms revealed that, during the same period, several House Republicans received contributions from the Committee to Re-elect Barr _ including state Reps. Don Aldridge, Karen Mills and Jan Breuer, all among Health Committee members who voted 13-0 to pass the measure affecting NutraSweet. The trio received $1,500, $1,000 and $750 respectively from Barr, who for years has enhanced his influence by donating to colleagues' campaigns. (

_Barr and Arizona State University regent William Reilly contacted the school's president, J. Russell Nelson, and Academic Vice President Jack Kinsinger to inquire into Monte's public attacks on NutraSweet, published reports said. Kinsinger insisted that the issue caused no delay in his decision to grant Monte tenure. Barr did not return phone calls. (

_When Monte's first petition was rejected, and he filed for reconsideration, Hurwitz wrote a letter offering legal advice to the DHS about its response and sent copies to Barr and aides to Babbitt. (

_In April of 1985, about the same time Monte and his associates finally were to be granted a hearing before the state agency on their petition, they learned that the Arizona legislature had used a rare maneuver to change the law, without public notice, to bar state regulation of FDA-approved food additives. The measure passed under the misleading title of a toxic waste bill. (

Monte's campaign to ban NutraSweet in Arizona prompted the state Department of Health Services to conduct a study to determine how much NutraSweet soft drinks degraded in high-temperature conditions. The study, completed in July 1984, found that methanol levels were highest, 9.4 parts per million, in Diet 7-Up samples stored the longest time in the warmest temperature, 99-degree heat. (

Present and former Arizona state officials have told UPI that the study concerned DHS officials enough that they discussed a NutraSweet ban. (

But Norman Peterson, manager of the DHS's Office of Chronic Disease and Environmental Health Services, said that the agency concluded that ''the FDA had addressed the methyl alcohol question and had all sorts of supporting data. We had no basis for saying that the data they had presented in support was not correct and adequate.'' (

Another source said Peterson was distressed enough that, during a meeting attended by DHS director Donald Mathis, he proposed being allowed to recommend that pregnant women and children limit their consumption of NutraSweet. (

Peterson would not confirm the episode, but recalled that he ''was upset about the fact that there were so many unanswered questions.'' (

Mathis, who since has left the agency, said he was satisfied that it ''wouldn't be humanly possible'' to ingest levels of NutraSweet that would produce a toxic reaction. (

In September 1984, Monte and his associates filed suit to force the DHS to impose storage and labeling requirements or ban NutraSweet altogether. But a proposed settlement under which the agency would hold a public hearing was scuttled because it lacked the approval of Mathis's successor, Lloyd Novick. ^ more(

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After more negotiations, the DHS agreed again to hold a hearing. But before it could take place, the issue was killed by the legislative change.(

House Speaker,James Sossaman later admitted that the GOP-controlled House violated its own rules in passing a so-called ``strike-all'' amendment. Chairman Bart Baker of the Health Committee engineered the action, in which an existing bill was stripped, replaced with the NutraSweet language and brought to a vote without the required 24 hours public notice.(

For Monte, the development was all the more staggering after he had gotten into a jam over his stock purchase.(

Monte said that, after reviewing files at the FDA and consulting with his lawyer in 1983, he invested less than $2,000 on Searle options _ hoping to raise money to support his costly legal battles against the sweetener. He said he ended up losing $1,224.(

Lawyer Rick Faerber also invested in part, he said, because of Monte's knowledge of an upcoming CBS story critical of the FDA's approval of aspartame. He said stock analysts had phoned Monte inquiring about his Arizona petitions and apparently got the idea the developments would depress the stock value.(

Faerber said he regrets telling Monte that he ``didn't think there was anything wrong'' with investing, particularly because pro-NutraSweet forces apparently learned of their dealings. CBS employees also bought ``put options,'' but a Securities and Exchange Commission investigation did not lead to any charges.(

Shortly after news stories about the investment appeared, Rep. Bob McEwen, R-Ohio, assailed CBS and Monte for ``irresponsible reporting and conflicts of interest'' in a brief speech on the floor of the U.S. House. McEwen charged that the ``false report'' about NutraSweet was aired solely for profit.(

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After more negotiations, the DHS agreed again to hold a hearing. But before it could take placq, the issue was killed by the legislative change. (

House Speaker,James Sossaman later admitted that the GOP-controlled House violated its own rules in passing a so-called ``strike-all'' amendment. Chairman Bart Baker of the Health Committee engineered the action, in which an existing bill was stripped, replaced with the NutraSweet language and brought to a vote without the required 24 hours public notice. (

For Monte, the development was all the more staggering after he had gotten into a jam over his stock purchase. (

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But in his speech, McEwen did not mention that his top assistant, Charles Greener, is the son of William Greener Jr., Searle's vice president for corporate communications. (

Charles Greener, who said he was ``unaware'' of McEwen's floor speech until after it occurred, said his father never has handled NutraSweet matters and that McEwen did not know any Searle officials. (
(

The success of the Searle family business, founded 80 years ago, is all the more astounding when compared to the company's predicament in 1977 when it plucked Rumsfeld as its president. Facing a company mired in debt, Rumsfeld, a native Chicagoan and former Illinois congressman, quickly hired three other outgoing Ford administration officials to join him. (

As executive vice president, he named John Robson, a former partner in the Chicago law firm of Sidley & Austin who had served as President Ford's chairman of the Civil Aeronautics Board. Robert Shapiro, Robson's special assistant at the Transportation Department, was tapped as general counsel. Rumsfeld also hired William Greener Sr., who had been a spokesman in the Ford White House and Rumsfeld's chief spokesman at the Pentagon. (

The pharmaceutical company suddenly was being run by lawyers and politicians. (

Stomaching a $28 million net loss in his first year, Rumsfeld slashed Searle's operations, selling off more than 30 subsidiaries worth more than $400 million. (

Before Rumsfeld could mount a full-scale effort to lift an FDA freeze on the sale of NutraSweet, Searle was hit with serious new problems. Suits filed on behalf of 780 women alleged the company's Copper 7 intrauterine device had caused them to develop pelvic inflammatory disease, an infection of the reproductive tract that can lead to sterility, even death. (

Before the suits could be settled, Searle sold out to Monsanto. (

The huge, St. Louis-based chemical company and its officers promptly were met with stockholder suits alleging they had failed to explore potential safety problems with Searle's biggest moneymakers _ the Copper 7 IUD and NutraSweet. (

Rejecting criticism of the acquisition, Earl Harbison Jr., executive vice president of Monsanto and chairman of the board of its Searle pharmaceutical subsidiary, said in October 1985 that Monsanto ``studied this situation (the Copper 7 litigation) very closely prior to acquiring Searle, including consultations with independent physicians.'' (

``We satisfied ourselves with the safety and efficacy of the product,'' he said. (

Since then, the Copper 7 has been pulled off the market. Some lawyers likened the resulting legal morass to the failure of the Dalkon Shield that drove the Richmond-based A.H. Robins Co. into Chapter 11 bankruptcy protection. (

But a former Monsanto official, who requested anonymity, said that as part of the sale agreement, Searle set aside reserves to cover the IUD lawsuits. (

Thanks to NutraSweet, Searle family members Daniel and William Searle and their sister, Suzanne Searle Dixon, to date appear to have walked away unscathed from all the crises and legal battles. (

And even if NutraSweet were proved hazardous, the purchase agreement provided ``no escrow, reserve or holdback for liability stemming from the potential health hazards attributed to the NutraSweet product line,'' says one lawsuit filed by Chicago lawyer Robert Holstein on behalf of a Monsanto stockholder. (

And Rumsfeld emerged from his nine years with the company in solid financial condition. Securities and Exchange Commission records show that for his guiding the sweeping turnaround, he earned more than $2 million in salaries and more than $1.5 million in bonuses between 1979 and 1984. ^ adv for wed oct 14 and thereafter(

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Putting on the blitz: The selling of a sweetener(
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By GREGORY GORDON=

WASHINGTON (UPI) _ ``Banana plants don't make NutraSweet,'' the television announcer noted wryly, and the image of an exotic bird perched in a jungle tree filled the screen. (

``Neither do cows,'' said the voice, as the camera cut to a robust-looking heifer wagging its tail. ``But they might as well. If you've had bananas and milk, you've eaten what's in NutraSweet.'' (

True _ bananas, milk and NutraSweet all contain phenylalanine, one of 21 amino acids that form the ``building blocks'' of protein. But that doesn't tell the whole story. (

Dr. Richard Wurtman, a neuroscientist at the Massachusetts Institute of Technology, says that because NutraSweet lacks other important amino acids normally found in foods, the brain absorbs unusually high levels of phenylalanine that could increase the likelihood of epileptic seizures. (

Referring to an ad proclaiming that the body treats the ingredients of the artificial sweetener ``no differently than if they came from a peach or a string bean or a glass of milk,'' Wurtman said, ``That's not true.'' (

Dr. Louis Elsas, director of medical genetics at Emory University, groans at industry arguments that eating or drinking NutraSweet, known generically as aspartame, is just like eating a hamburger. (

``Phenylalanine is a known toxin to the brain,'' Elsas said. ``Aspartame is phenylalanine and drinking aspartame is like drinking phenylalanine as an individual amino acid.'' (

A spokeswoman at the New York offices of Ogilvy and Mather, the lead ad agency on the sweetener account for the Chicago-based NutraSweet Co., declined comment on the allegations. (

The drumbeat of NutraSweet advertisements has been steady. Beverage Industry, a trade publication, labeled the NutraSweet blitz ``probably the largest advertising campaign ever designed around a product ingredient.'' (

Industry sources say that since 1984, The NutraSweet Co. alone has spent $30 million to $40 million a year on advertising, and ads by diet soft drink manufacturers and other companies whose products carry the swirl trademark of the sugar-free sweetener would easily send the figure past $100 million a year. (

The campaign has worked to make NutraSweet a household word. (

Football stars Joe Montana and Dan Marino and boxer Marvin Hagler have pitched products containing the artificial sweetener on television. Former Democratic vice presidential candidate Geraldine Ferraro has appeared in advertisements endorsing a product containing NutraSweet, as have numerous celebrities, including Bill Cosby, Raquel Welch and Billy Crystal. (

Children, who some scientists say may be particularly susceptible to ill health effects linked to NutraSweet, are a primary target of the NutraSweet hype. In one ad, for a NutraSweet-flavored vitamin, a curious child asked his mother, ``Why don't they put NutraSweet in broccoli?'' (

Although not in broccoli, the sweetener flavors scores of products ranging from coffee, cereal, chewing gum, cocoa mix, diet sodas and iced tea to gelatins, puddings, whipped toppings and vitamins. (

The campaign to sell NutraSweet marked the first time a brand-name ingredient, rather than a product itself, has been so extensively advertised, industry observers said. (

The NutraSweet campaign began with a highly sucessful theme of ``why some things taste better than others,'' touting NutraSweet's flavor. But in 1985, after the first serious scientific concerns were raised, the thrust of Searle's advertising shifted abruptly to a controversial new theme boasting that the sweetener is as safe as naturally grown foods. (

Today, NutraSweet ads often appear during commercial breaks in TV fitness programs. ^ adv wed oct 14 or thereafter(

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STATEMENT OF SHANNON ROTH
FOUNDER OF
ASPARTAME VICTIMS & THEIR FRIENDS

I would like to thank you for the opportunity to be a participant in these crucially important hearings.

Because of my ingestion of the chemical sugar substitute, aspartame/NutraSweet, I am permanently blind in my left eye. This incident has changed the present and future of my whole life. Never again, will I take any gift from God for granted as I did my eye sight.

With this sudden, overnight loss of vision, came numerous medical examinations, diagnostic testing, medication and a hospital stay of 5 days.

In the very beginning there was no known cause for my problem. There were many causes ruled out by tests and symptoms or lack of symptoms. Thankfully, brain tumor, an anyerism pressing on the optic nerve, diabetes, multiple sclerosis, and a viral disease were dismissed.

For nearly 18 months prior to my sudden vision loss, I had been ingesting continual amounts of NutraSweet in all foods requiring sugar. My use was not clouded by knowledge of controversy of safety, descrepencies in manufacturer's laboratory testing, nor did I have any knowledge of an effort by certain consumer advocates and scientists to keep this product off the market. Instead, I had a confidence in NutraSweet that had been lost in saccharin because of news of evidence of cancer risks.

The summer of 1984 was a particularly difficult one for me as I remember terrible crashing headaches, never being able to remember the simplest thought or request after it left someone's mouth, sleepless nights, being paranoid around my close friends and family, exhibiting personality changes no one could explain, and just feeling my life had ebbed at age 36. Things were definitely out of sink, but I had everything any person could have wanted; a wonderful family, close friends, a business of my own, a lovely home and a successful marriage.

It is no wonder that the possibility of NutraSweet causing my blindness was never even fathomed, much less discussed. The precluding symptoms were chalked off to stress. I was a normal, healthy human.

You can imagine my distress when I learned in an off-handed manner that there was a controversy over this product that I loved and trusted so much. A friend told me of someone who went through the same illness I had suffered and this person had discovered that NutraSweet was the culprit in time to regain over

80% of her vision. I was not so fortunate.

After discovering an opthalmologist, Dr. Orion T Ayer, who had diagnosed a friend with NutraSweet poisoning, I was seen by him and was told that it was the probable cause of my blindness as well.

Dr. Morgan Raiford, known for his expertise in identifying methyl alcohol damage to the eye, concurred.

It was at this time I gave my original physician, Dr. Earl Wingo, these two opinions and supporting data. He was able to agree that this was more than likely the cause of my loss and the probability should not be dismissed.

Getting to this point was not easy for my husband and myself. Michael (my husband) did the research since I was still not up to my full potential. He found that there was no central resource to gain any information on the subject of NutraSweet.

The manufacturer was adamant that their product could not have had this affect on me. The FDA quoted themselves as approving the "most tested food additive in the history of the FDA".

He was persistent and found others who were aware of the situation as a major health problem.

As a result of our difficulties in gathering information and our anger and shock that this could happen in the first place, we were impassioned to come to Washington in July of 1985 and announce the formation of Aspartame Victims and Their Friends.

Our purpose was to distribute information we had about the hazards of aspartame, collect symptoms and count the number of Americans who had been damaged by this unnatural sweetener.

Michael was and has been so generous in financially supporting my efforts to organize and keep the group running. We have received a few donations over the past three years from other victims who want to keep the torch burning, but the major every-day expense has been our own. We have never received or even entertained the idea of receiving any funds from any special interest group such as the sugar or saccharin industries.

I was amazed by the response I received. We never had the luxury of being able to advertise the fact that there was now a consumer hot-line set up to report complaints about a food additive. Yet, in that first year, we received around 400 responses. At the time, I remember being overwhelmed by the fact that the FDA had only gotten a few more than that since the spring of 1984.

The number has now tripled, and the symptoms are far more serious than when we started out. That is, the majority of the letters or phone calls we receive, describe seizures which have wrecked

the individual's life, vision loss or severe eye damage that has also destroyed normal functioning in many cases, constant nausea and dizziness to the extent that a person cannot live a normal existence, depression so severe it has nearly led to suicide and in two cases did.
Many of those who have suffered are now acutely aware, after the fact, that the cause was aspartame. In most cases the symptoms disappeared when Nutrasweet consumption was stopped and reappeared on rechallenge. Only the permanent damage to fragile nerve fibers remains, in many cases never to be healed.

I am able to realize how fortunate I am when I speak to a lady, desperate to know why she has lost vision in one eye and now 6 months later she is experiencing the same horror over again, only now it is her other eye. She tells me of her plight with doctors and mounting medical bills and because of one doctor's poor diagnosis she has now been denied medical insurance. Her sight is so deteriorated she must read with a magnifying glass and cannot drive. She lived on NutraSweet for almost 2 years.

Only recently, I received a graphic letter from a nursing student who was using aspartame-containing products and did not know that each time she drank another diet soda she was having a toxic reaction so severe that she would pass out and not comprehend for how long. She suffered an attach while at college and so her parents were notified. Her mother, not knowing any better, was soothing her with a continual offering of diet sodas. Her condition became so violent that she even had spells while driving on the freeway. Knowing the feeling that was coming over her, she was able to pull off to the shoulder of the road, stop her car just in time to fall over the wheel out like a light. She discovered, while in the hospital and not being given her usual dosage of aspartame, that there was a connection between the reaction and the diet soda a visitor brought to the hospital. Immediately, the reaction began and her doctors were able to pinpoint her trouble.
Most are not this lucky.

Can you imagine being so dizzy and nauseated that you cannot even comb your hair? This was the story of a lady who drank diet coke to calm her nausea. She knew she was sick, very sick, yet the doctor could find nothing wrong with her. Trip after trip to his office gained her nothing except more bills. She said she was so miserable she wanted to die. The revelation that NutraSweet could be causing her trouble was enough to convince her to toss the diet Coke bottle out the window and today, 2 years later, she can feel like a normal person again.

When a mother calls me to tell me about her baby who suffered a seizure while she was breast feeding and at the same time drinking a diet coke, I know there is not enough being done to stop tragedies.

Another calls and tells of her two year old son, who she feeds

Another calls and tells of her two year old son, who she feeds NutraSweet to, especially Diet Coke. He has had a seizure 10 minutes after she gave him a NutraSweet-filled Tylenol tablet to reduce a fever. She said the doctor had no clue as to why the child had the seizure. There was no evidence he could find medically. He was not aware of the aspartame controversy.

The doctor is unaware of the information that NutraSweet has been associated with seizures and a mother is giving her toddler a diet of sugar substitute chemicals. Why? How can this type of scenario go on.

The public is being held hostage. The medical profession is being hoodwinked. The public hears and sees commercials and ads supported by a $32 million advertising budget, telling us NutraSweet is a protein and is made from bananas and milk, while the medical profession is sent letters by the manufacturer to head off the patient who will come in to complain about possible reactions to its product. The manufacturer tells the doctors there could not possibly be any toxic reaction associated with NutraSweet.

There is a huge clinical study being done in the laboratory of the American marketplace.

This is shocking, criminal and most of all dangerous. Whether we choose to use this chemical sweetener or not we may not escape damage.

The pilot of the commercial airliner you and your family are flying or the driver of the car coming directly toward you could be ingesting it and have a sudden seizure. You are in immediate danger.

What about the pharmacist who is mixing your prescription for you? What if he is suffering memory loss or debilitating headaches because he uses aspartame? You are in immediate danger.

If the nurse caring for your loved one is giving that loved one an injection of a very powerful drug and may not remember she had already given her patient his injection, your loved one is in immediate danger because she is suffering from aspartame poisoning.

We must realize that this is not a small problem of a few so-called sensitive individuals. It is a large, horrible, growing problem which touches virtually everyone.

Please take time to consider personally how you could be affected and please take time to act on your feelings.

Our hot-line is not enough to solve this problem. We would like to see a federally funded one set up and see it advertised

The research situation is in need of immediate attention. Money for independent research should be generous. There are many brilliant, unbiased scientists who need funds to do much needed research. There are areas in the research field which have not been explored. We are very uncomfortable with the fact that all research reports funded by the NutraSweet Co. or Monsanto Corp. continually demonstrate no adverse reactions while independent research usually shows serious adverse reactions.

Until other steps can be taken, the American public should be protected by knowledge of exact amounts of aspartame in each product purchased. The manufacturers should be made to divulge even the smallest amount of this chemical when it is added to any product that goes into our mouths. Aspartame is now in children's Tylenol (as well as other brands of children's acetaeminophens) and toothpaste and is not labeled because of drug laws which allow pharmaceuticals to not list inactive ingredients in drugs. (Yes, toothpaste is a drug, according to an FDA spokesman.)

In closing I would say that this is only a small view of the big picture. Unfortunately it is a big picture which is growing faster and faster each and every day. You have the opportunity to save many from suffering. Please do all that is in your power to stop any more pain.

ATLANTA EYE CLINIC, P.C.
615 PEACHTREE STREET, N.E.
ATLANTA, GEORGIA 30308
(404) 872-4701

Stewart Atkinson, M.D.
John L. Humphreys, Jr., M.D.
Morgan B. Raiford, M.D.
Louis Berger, M.D.

The Honorable Howard M. Metzenbaum
Labor and Human Resources Committee
140 Russell Senate Office Building
Washington, D.C. 20510

Dear Senator Metzenbaum,

Enclosed is the outline regarding the toxicity of neutrasweet (Aspartame). This product has serious side effects from human consumption and should not be used in the market place.

Sincerely,

Dr. Morgan B Raiford

Dr. Morgan B. Raiford

The Honorable Howard M. Metzenbaum
Labor and Human Resources Committee
140 Russell Senate Office Building
Washington, D.C. 20510

Dear Senator Metzenbaum,

I had the opportunity, in Atlanta, Ga., to see the effects of methyl alcohol toxicity in 1952- 1953 which resulted in visual damage to the optic nerves and retina in over 300 cases and the deaths of over 30 persons.

I examined Shannon Roth on July 7, 1986, along with several other patients. I observed evidence of effects in her eye and the eyes of the other patients that were comparable to the effects observed in the patients who suffered methyl alcohol toxicity in 1952-1953.

There was damage in the central fibers, 225,000 of the total 137,000,000 optic nerve fibers. (resulting in optic nerve atrophy) in her case, which would be comparable to that observed from patients suffering methyl alcohol toxicity. The extent of damage to these fibers would explain partial to total blindness.

The macula area of the retina and optic nerve fibers are highly reactive to the toxicity of methyl alcohol because these fibers and nerve cells require from four to six times as much oxygen and nutrition as the visual pathways peripheral nerves. These fibers and nerves (rods and cones) cannot go with out oxygen for more than 90 seconds without some visual loss. Aspartame is broken down by the upper portion of the digestive tract and methyl alcohol is then absorbed into the blood vessels of the region which travels through the bodies' entire vascular system. This toxic effect causes extensive damage to the human visual pathway, ending with optic nerve atrophy as well as retinal starvation and visual loss. The intensity of these toxic effects from the methyl alcohol spin-off causes impaired nerve damage that varies with intensity as to the amount of methyl alcohol the individual absorbs.

Each eye will react differently to this kind of involvement. In large doses of consumption of methyl alcohol the differences in response might not be noticeable, although, cases of damage in one eye from methyl alcohol have been reported in the literature.

But in the kind of chronic low dose exposure to methyl alcohol experienced by Shannon Roth (in NutraSweet consumption) and other NutraSweet consumers, it is likely that they would experience the impact on the optic nerve differently in each eye.

The important point is that the damage observed in Shannon Roth's eye was identical to the damage I observed repeatedly in the eyes of individuals whose eyes have been damaged by methyl alcohol toxicity.

Sincerely,

Dr. Morgan B. Raiford

Morgan B. Raiford, M.D., B.S., M.Sc Med. Ophthalmology, D.Sc Med. Ophthalmology, D.H.L., Am. B. Ophthalmology, Am. College Nuclear Med.

ORION T. AYER JR., M.D., P.A.
THE RETINA INSTITUTE
MEDICAL AND SURGICAL DISEASES OF THE
RETINA AND VITREOUS
DIABETIC EYE DISORDERS

P.O. Drawer 16007
3900 Central Avenue
Suite A
St. Petersburg, Florida 33733

Telephone
(813) 327-1475

1236 East Druid Road
Clearwater, Florida 33516

October 28, 1987

To Whom It May Concern:

Re: Shannon Roth

Mrs. Roth was first examined by me approximately two years ago. At that time she was diagnosed as having optic atrophy and decreased vision in one eye. The other eye was unaffected. All the available medical tests were performed and showed no evidence of an associated neurologic deficit.

Mrs. Roth had been using aspartame in relatively large doses during the time that she experienced visual difficulties. Myself and other doctors question the possibility of aspartame and its breakdown products as being a possible etiologic agent. In reviewing much of the literature available, the presence of methanol even in relatively small quantities can cause neurologic damage in susceptible individuals.

There appears to be considerable controversy concerning nutrasweet. Some of the original investigators who were instrumental in the FDA approval maintain that it is harmless. Certainly, most food additives including MSG and saccharin were thought to be harmless at the time of their introduction. The request for an objective reevaluation of any substance widely used that could have the potential for harmful effects should be welcomed.

In conclusion, my opinion is that aspartame containing agents can in selective cases be neurotoxic. Mrs. Roth's particular case may indeed be one of many patients who is more sensitive to this additive.

With best regards,

Orion T. Ayer, Jr., M.D.
OTA/PSI3

Dictated but not read to expedite delivery.

Marcia E. Young
5 Heather Lane RR1
Lyme, NH 03768
(603) 643-9312

September 25, 1987

Food and Drug Administration
5600 Fishers Lane
Rm 13-62
HFC-161
Rockville, MD

Dear Sirs:

I am writing this letter as a concerned parent, biochemist and co-author of THE RIGHT START - a book on infant feeding and chronic disease prevention (Walker and Company, New York, 1987).

As a biochemist, I have long been aware of the potentially harmful side effects of NutraSweet (aspartame). As a mother, I have been especially cautious to protect my children from this hazard. And as an author, I have tried to explain why aspartame should not be consumed by pregnant or lactating women and by children under age four. I find the FDA's failure to caution this extremely vulnerable segment of the population about the dangers of NutraSweet to be highly irresponsible and bordering on negligence.

This letter has been prompted by a personal experience I would like to relate to you. I would like this story to be officially documented in your file of aspartame side effects. For confirmation, you can contact my neighbor, Sarah Alpert of Heather Lane in Hanover, NH (603) 643-6836. If you need additional information on this matter, feel free to contact me at the above address.

> We recently moved to Hanover, NH and as a get-acquainted gesture, I invited my neighbor Sarah, her three year old and newborn to lunch.
>
> As a matter of small talk, I asked how her new baby was. Quite exasperated, she said, "If you'd asked me that a week ago, I would have said 'wonderful', but for the last week he's been inconsolable. He cries all the time, is up all night fretting and hasn't given us a moment's

> peace."
>
> I knew she was breastfeeding, so I asked if she had changed anything in her diet in the last week. She didn't think so.
>
> In a while, she nursed the baby and within a few minutes, he began crying frantically. We tried all the usual manuevers to soothe colicky babies - nothing seemed to work.
>
> Then a light flashed in Sarah's mind. She had begun drinking NutraSweet just a week ago!
>
> I surmised that Matthew probably had a headache (the most common side effect of aspartame) and applied a cold facecloth to his forehead. Within minutes, he fell blissfully to sleep.
>
> Sarah eliminated NutraSweet from her diet and Matthew returned to his former good nature.
>
> Weeks elapsed without incident. Then, caught in a chocolate fit with nothing in the house but aspartame-sweetened hot chocolate, Sarah succumbed, rationalizing that we didn't know for sure if NutraSweet was the culprit. Within minutes of nursing, Matthew again went into uncontrollable crying.

This incident proves to me without doubt that parents should be warned of the potential problems of NutraSweet consumption. Sarah is an intellegent, concerned and well-educated mother. She believed that NutraSweet was as natural as 'bananas and milk' and would never have made the connection between her diet and her infant's distress if she had not met me at this fortuitous time.

Sarah related this story to her pediatrician who was equally unaware of the potential problems. This confirms the fact that information about the side effects of NutraSweet is not being sufficiently publicized. Even physicians are not getting the word.

How many other nursing babies are being unknowingly tortured by the lack of a warning label on aspartame products? Many breastfeeding mothers, being particularly sensitive to the extra weight they have gained during pregnancy, sweeten their foods with aspartame. Colic and the normal functional stresses in the newborn are difficult enough for parents to deal with without adding another variable.

In addition, many pregnant women rely on this sweetener to curb weight gain during pregnancy. Given what we know about phenylalanine in the brains of newborns with PKU disorder, and the permanent and serious consequences of excess phenylalanine at this vulnerable stage in neuro-development, I find it incredible that the FDA has not taken action to warn pregnant and lactating women of this potential hazard.

I am also alarmed at the increasing number of children's products - from Jello to vitamins - which portend to be "safer" for your children than sugar. I feel very strongly that we can not extrapolate conclusions from adult safety data to determine aspartame's safety in the rapidly developing brains of small children. And we certainly can not use it to determine safety to the fetus.

I urge you to seriously consider requiring warning labels on all aspartame products describing the well-documented side effects, as well as cautioning pregnant and lactating women and children under four that insufficient information exists to confirm aspartame's safety for this population group. Not to do so, in my mind, is medical negligence.

Very truly yours,

Marcia E. Young

cc. Richard Wurtman
M.I.T.

Juvenile Diabetes Foundation International
432 Park Avenue South, New York, New York 10016-8013. 212-889-7575. Telex (RCA) 238 790 NYKUR. FAX: 212-725-7579
EXECUTIVE OFFICE

Testimony of the

JUVENILE DIABETES FOUNDATION INTERNATIONAL

Presented by

Joan Beaubaire
International President

Regarding

ASPARTAME SAFETY

before the

Senate Labor and Human Resources Committee

November 3, 1987

JDF INTERNATIONAL IS A TAX-EXEMPT, NOT-FOR-PROFIT ORGANIZATION

My name is Joan Beaubaire; I am the President of the Juvenile Diabetes Foundation International (JDF). JDF is an international voluntary health organization composed of over 160 chapters nationwide dedicated to supporting research which will cure diabetes and alleviate its devastating complications and improve the quality of life of this nation's 12 million diabetics. As the largest organization of diabetic consumers in the world, JDF is concerned with the benefits and risks of non-sugar sweeteners such as aspartame.

Our perspective with respect to this issue is unique. The insulin-dependent diabetic is required to control his intake of sugar and his blood sugar levels. As such, in collaboration with his family and a team of health care professionals, he is subject to a specially designed dietary regimen. Although diets may be individualized, eating is a social activity, particularly for the youngster in school. Passing up candy corn at Halloween, soft drinks at the fast food outlet, and cakes with sugar frosting at birthday parties are the kind of deprivation a diabetic child must endure. These restrictions impede the ability of the diabetic child to assimilate and intensify his feelings of being "different" from his peers. Non-sugar sweeteners like aspartame provide the diabetic with the ability to control his intake of sugar when circumstances conspire to force him off an established dietary program. The enhanced availability of non-sugar sweeteners has assisted millions of diabetic children cope with difficult social situations and thereby more easily accept and deal with this chronic disease.

Because our children depend heavily upon these sweeteners, and hence may have higher levels of consumption than the population at large, we remain particularly vigilant about ensuring that non-sugar sweeteners are safe for human ingestion. Concerns about the safety of aspartame have been raised since its manufacture initiated the process of securing approval from the FDA for the marketing of the product over a decade ago. The safety of aspartame is accepted throughout most of the world, and millions of Americans consume products containing aspartame every day. The Food and Drug Administration has devoted years of analysis to the evaluation of the product, both prior to, and subsequent to its approval of aspartame for a multitude of uses. The agency substantiated the accuracy and reliability of the studies upon which it relied in granting approval. It has convened a public board of inquiry which confirmed the safety of aspartame and the appropriateness of its approval.

The General Accounting Office (GAO) was asked to determine if FDA appropriately followed its required process in approving the product. In June, 1987, GAO issued its final report, concluding that:

> FDA adequately followed its food additive approval process in approving aspartame for marketing by reviewing all of Searle's aspartame studies, holding a public board of inquiry to discuss safety issues surrounding aspartame's approval, and forming a panel to advise the Commissioner on those issues . . . Throughout aspartame's approval history GAO found that FDA addressed safety issues

> raised internally and by outside scientists and concerned citizens . . . GAO believes that FDA's and other scientists' planned and ongoing research, and FDA's monitoring of adverse reactions, should provide FDA with the basis for determining what future actions, if any, are needed on aspartame.

Based upon this extensive review, we believe that aspartame is an appropriate non-sugar sweetener for the diabetic diet. Moreover, we have an extensive communications network with our membership, representing tens of thousands of diabetics who utilize aspartame. Those few comments we receive from diabetics generally follow media accounts of non-sugar sweetener developments, like Congressional hearings or FDA developments, and are rarely reports of suspected personal adverse reactions to aspartame use.

The foundation for these hearings is the Committee's attempt to ascertain whether aspartame is safe. We recognize that, unfortunately, no food or drug is totally safe for every individual. We cannot be assured that each individual can utilize a food product and be guaranteed freedom from adverse reaction or complaint. As consumers, we must make an informed decision as to the use of a product based upon the judgments of those charged with maintaining the public health -- the Food and Drug Administration; health care professionals; an industry which must present extensive clinical evidence as to the safety and effectiveness of the products for which it seeks approval; and the community of independent scientific investigators. After more than a decade of debate -- within Congress, the

Executive Branch, and the medical community -- we have confidence in FDA's conclusion that aspartame is a safe food additive and one which we believe is useful in the management of diabetes.

Our organization is pleased that there will be ongoing study relating to the safety and appropriate use of aspartame. We believe that FDA should take whatever steps are appropriate to ensure that its Adverse Reaction Monitoring System (ARMS) appropriately catalogues and, in selected cases, investigates complaints sent directly to the agency or referred to it by the manufacturer, physicians, scientists, or others. Finally, in those instances in which documented clinical problems associated with aspartame appear to occur with some degree of regularity requiring further investigation, we would strongly encourage FDA, Congress, and the industry to expeditiously effectuate resolution of these issues in a manner which will not precipitate alarm and anxiety among diabetics who have a special need for non-sugar sweeteners.

In light of the foregoing, the Juvenile Diabetes Foundation International is satisfied that aspartame should remain available in the marketplace.

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FOUNDATION, INC.

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November 2, 1987

Senator Orrin G. Hatch
Committee on Labor and
Human Resources
SR-135 Russell Senate Office Bldg
Washington, D.C. 20510

Dear Senator Hatch:

I am writing to you as a diabetic and as an Hispanic concerned with the critically high incidence of diabetes among Hispanics. A recent study by the University of Texas Medical School in my home town of Laredo, Texas reported that 40 percent of the population in the city is known to have diabetes and another 10 to 20 percent are afflicted but not yet detected. Over 90 percent of the population of that city is Mexican American.

Throughout the southwest, hospitals have reported that almost half of all the Mexican American patients admitted are diabetic and most of them didn't know it. Another more recent study conducted by the National Center for Health Statistics found that Mexican Americans have the lowest access to medical care.

The high incidence of diabetes among Hispanics combined with the low accessibility to medical care creates a deadly combination. As you know, diabetes is a treacherous disease. It is painless, and its symptoms are so insidious that it can go undetected until serious and irreversible complications are detected. As a result, kidney disease, loss of sight and amputations are substantially more common among Hispanics.

On the other hand, diabetes can be managed and its damage reduced by controlling body sugar through diet, exercise and medication. But it's not as easy as it sounds. Eating habits established over generations are not easily changed. One product which recently became available is helping to modify our diets by reducing the intake of sugar. That product is aspartame. Aspartame is the main ingredient in NutraSweet. Its taste is so similar to sugar that I now prefer products with aspartame rather than other artificial sweeteners. NutraSweet has helped me reduce my intake of sugar substantially and has helped me reduce my dependence on medication. I hope that others who use it are able to report the same results.

I am writing to you because I have heard that the Senate Labor Committee has scheduled hearings on aspartame.

400 First Street N.W. Suite [illegible] Washington D.C. 20001 • [illegible]
An affiliate of the League of United Latin American Citizens, Inc.

Page Two

Despite its acceptance by scientific and regulatory bodies throughout the world, by the Food and Drug Administration, and by numerous scientific institutes in our own country, some people still have doubts that aspartame is completely safe for them. That is their right. I, on the other hand, am comfortable with the FDA approval and the endorsements by the American Diabetes Association, the Epilepsy Institute and the Journal of the American Medical Association. Unless credible scientific facts are provided to disprove these findings, I will continue to use aspartame. I respectfully request that my views expressed in this letter receive due consideration during the hearings on aspartame.

Sincerely,

Eduardo Peña Jr.

Eduardo Peña Jr.

STATEMENT OF ROBERT H. KELLEN
PRESIDENT, CALORIE CONTROL COUNCIL
SUBMITTED FOR THE NOVEMBER 3, 1987
SENATE LABOR & HUMAN RESOURCES COMMITTEE HEARING ON ASPARTAME

The Calorie Control Council and its members appreciate the opportunity to provide this statement to the Committee. We ask that it be included in the official hearing record.

The Calorie Control Council is an international association representing 60 manufacturers and suppliers of dietary foods and beverages. Our membership includes the manufacturers of more than a dozen different dietary sweeteners, as well as the food and beverage companies that utilize low-calorie sweeteners in hundreds of different low-calorie products.

Since its inception in 1966, the Council's philosophy has been to support the development and availability of a variety of safe low-calorie sweeteners for use in the food supply. A careful attention to scientific research has been a cornerstone of the Council since its founding. Based on a thorough review of the scientific evidence, the Council is confident of the safety and benefits of aspartame.

Since its initial approval by the Food and Drug Administration in 1981, aspartame has established itself as an important component in many low-calorie, sugar-free foods and beverages. Currently, more than 100 million people around the world consume aspartame-containing products.

People consume low-calorie products for a variety of reasons, the most popular being to stay in better overall health, to reduce weight and to control weight, according to a national survey.

The rapid rise in aspartame's popularity can be attributed to the many benefits aspartame provides to calorie-conscious consumers, including:

- Aspartame has a clean sweet taste, which taste-test panels have shown to be very similar to the taste of sugar.
- Aspartame does not promote tooth decay.
- Aspartame enhances and extends flavors.
- Aspartame helps consumers control caloric intake. By substituting aspartame for caloric sweeteners in foods and beverages, calories can be reduced substantially, and in many products practically eliminated.
- Aspartame is acceptable for diabetes management.

Since aspartame was approved, FDA has repeatedly reviewed requests for a stay of the sweetener's approval and for a new hearing on aspartame safety issues. In February 1984, FDA denied requests for a public hearing in a published opinion, noting that aspartame's critics had not presented any unresolved safety questions. FDA's action was affirmed by the U.S. Court of Appeals in Washington in 1985.

Last November, FDA again denied a petition for aspartame's removal from the market. In denying the petition, the agency noted the "extensive data" supporting aspartame's safety. It added, "It is likely that no food product has ever been so closely examined for safety" and that its decisions to approve aspartame "have been given the fullest airing that the legal process requires."

A number of anecdotal reports have suggested that some consumers have alleged adverse reactions following consumption of products containing aspartame. However, there is no conclusive scientific evidence that aspartame is linked to adverse reactions in humans. Additionally, in none of the consumer complaints that have been reported to FDA has it been established that the reported reactions were causally related to aspartame.

The Centers for Disease Control also has reviewed more than 500 consumer complaints related to the use of aspartame. The CDC found that the consumer complaints it has reviewed "do not provide evidence of the existence of serious widespread, adverse health consequences attendant to the use of aspartame." The CDC further noted that "the majority of frequently reported symptoms were mild and are symptoms that are common in the general populace." FDA continues to review consumer complaints and focused clinical studies are being conducted to identify any possible small subgroup sensitivities to aspartame.

A recent development which yielded yet another independent favorable assessment of aspartame is the General Accounting Office (GAO) June report on the FDA approval process followed for aspartame. The report concluded that "FDA adequately followed its food additive approval process in approving aspartame." It further noted, "Throughout aspartame's approval history, GAO found that FDA addressed safety issues raised internally and by outside scientists and concerned citizens." The investigation by GAO, an agency of the U.S. Congress, was conducted at the request of Senator Howard Metzenbaum.

FDA has repeatedly affirmed its decision to approve aspartame, and now its process has been confirmed by GAO, as it was by the U.S. District Court of Appeals in 1985. It should be reassuring to the millions of aspartame consumers that our judicial system, and now the investigative arm of our legislative system, have upheld FDA's comprehensive review of aspartame's safety.

Due to aspartame's popularity and the number of products containing it, questions have been raised concerning aspartame consumption levels, particularly whether or not individuals may exceed levels considered safe. The Acceptable Daily Intake (ADI) for aspartame set by FDA and reevaluated and reaffirmed several times is 50 milligrams of aspartame per kilogram (mg/kg) of body weight. (FDA defines an ADI as the amount of a compound that can be safely consumed each day on a chronic, lifetime basis.)

Aspartame's ADI is based on a broad array of data. The data include clinical studies in which humans who received single doses of aspartame up to 200 mg/kg of body weight -- equal to consuming 70 cans of aspartame-sweetened soft drink in one sitting -- showed no ill effects.

FDA continues to monitor aspartame consumption data, which is compiled by an independent market research organization and submitted to FDA on a monthly basis. This data has shown that consumption of aspartame, for all age categories, is well within the range expected by FDA. Thus current consumption of aspartame is considerably below the level set by FDA which can be safely consumed for a lifetime, i.e., the ADI. FDA recently noted that "all post-marketing surveillance data concerning actual consumption [of aspartame] indicate that even high level consumers are well within the established ADI."

In addition to FDA, the Joint Expert Committee on Food Additives of the World Health Organization, the Scientific Committee for Food of the European Economic Communities, and regulatory agencies in more than 60 countries have reviewed aspartame and found it safe for use. The American Diabetes Association, American Dietetic Association, and American Academy of Pediatrics' Committee on Nutrition are among the health/medical organizations to issue statements in support of aspartame. A report published in 1985 by the American Medical Association concluded that the use of aspartame by normal individuals "is safe and is not associated with serious adverse health effects."

The Food and Drug Administration and most scientists who are familiar with the data conclude that aspartame, and its use in a wide variety of products, is a safe and useful option for those individuals who prefer a low-calorie sweetener.

When FDA approved aspartame in 1981, FDA Commissioner Hayes noted: "Few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety." The Calorie Control Council believes Commissioner Hayes' conclusions are just as true today as in 1981 -- and are further supported by recent research and repeated scientific and regulatory affirmations of aspartame's safety.

As the General Accounting Office confirmed in its June report, FDA has addressed safety issues raised against aspartame throughout the sweetener's approval history. FDA's continuing review of consumer complaints and its ongoing analysis of consumption data, as well as the focused clinical studies being conducted in an attempt to identify any possible sensitivities to aspartame, illustrate that the agency continues to monitor and regulate aspartame's use by American consumers in a prudent manner.

GAO stated in its report: "Because FDA followed its required process in approving aspartame and monitors adverse reactions and ongoing aspartame research, GAO is making no recommendations." GAO added that these regulatory activities "should provide FDA with a basis for determining what future actions, if any, are needed on aspartame." We believe the Senate Labor & Human Resources Committee should come to the same conclusion.

**American Council
on Science and Health**

December 3, 1987

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Elizabeth M. Whelan, Sc.D., M.P.H.
Executive Director
American Council on Science and Health
New York, New York

The Honorable Howard M. Metzenbaum
140 Russell Office Building
Washington, DC 20510

Dear Senator Metzenbaum:

The American Council on Science and Health strongly endorses the statements of Robert Shapiro, Nutrasweet Company's Chairman of the Board. Before its introduction into the American food supply, Nutrasweet underwent an unprecedented series of tests in both humans and animals. It has been approved for use by more than 60 nations and is ingested regularly by some 200 million people world-wide.

We at ACSH are satisfied that Nutrasweet is safe. There is nothing to be gained from legitimizing unfounded fears about this product; indeed, such claims only add to the general mistrust of industry and government that is already pervasive among American consumers. We suggest that, until and unless new scientific data raise questions about the safety of Nutrasweet--data that are founded on more than anecdotal reports in the consumer press--that the case on Nutrasweet be closed and that we start concentrating on genuine health threats, like cigarette smoking, AIDS, excessive drinking, and hard drugs. Only then will we truly make a difference in the lives of the people who look to us to guard public health.

Thank you for your time and consideration.

Sincerely,

Elizabeth M. Whelan
Executive Director

Enclosure: Introducing ACSH
Low Calorie Sweetener Booklet

Please Reply to:
☐ 1995 Broadway 18th Floor New York, NY 10023-5860 Telephone: (212) 362-7044
☐ 47 Maple Street Summit, NJ 07901-2560 Telephone: (201) 277-0024

Senator **Metzenbaum**. Thank you very much, Mr. Shapiro.

That concludes the hearing for today. We appreciate your working for us and look forward to working with you in the future.

Mr. **Shapiro**. Thank you, sir.

Senator **Metzenbaum**. There will be others, as well as the Chair, who will make submissions for the record.

[Whereupon, at 1:50 p.m., the Committee was adjourned.]

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